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Original Communications

AN AGGLUTINATIVE REACTION FOR HEMOPHILUS PERTUSSIS

I. PERSISTENCE OF AGGLUTININS AFTER VACCINE

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A MODIFIED technique of performing the agglutinative reaction with *H. pertussis* was described by us[1] in 1939. With this technique no agglutination occurred in the sera of 91 of 101 children with negative histories, but agglutination was demonstrated in the sera of 161 of 164 children who had received *H. pertussis* vaccine. It was observed that agglutinins stimulated by *H. pertussis* vaccine persisted in relatively high titer (usually over 1:160) for a period of at least three years.

Using the rapid technique of Powell and Jamieson,[2] Lapin[3] has recently reported finding agglutinins in the sera of patients three to five years after *H. pertussis* vaccination. Positive reactions were obtained in nine of seventeen individuals tested. Mishulow and her co-workers[4] have also recently noted the persistence of agglutinins in two individuals for from three to four years after vaccine. These observations have a counterpart in the case of the *Eberthella* typhi flagellar "H" agglutinins which have been described as persisting for from seven to fifteen years after typhoid vaccine.[5, 6] Somatic "O" agglutinins, however, are not so persistent.

The present paper reports further on the persistence of *H. pertussis* agglutinins following vaccine. The technique used was entirely the same as that previously reported. The strains present in the agglutinating antigen were changed usually every six to nine months and recently isolated (phase 1) strains used. Each antigen contained three to five strains—a concession to custom, as a monovalent antigen would probably have been satisfactory.[7]

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TABLE I

RESULTS OF AGGLUTINATIVE TESTS AFTER H. PERTUSSIS VACCINE

TITER	AT FIRST VACCINE	MONTHS AFTER FIRST INJECTION												
		>1 <6	> 6 <12	>12 <18	>18 <24	>24 <30	>30 <36	>36 <42	>42 <48	>48 <54	>54 <60	>60 <66	>66 <72	>72 <78
1:2560	0	2	4	3	3	3	3	0	2	0	0	1	0	1
1:1280	0	5	10	16	16	12	12	8	4	1	1	1	0	0
1:640	0	14	24	23	*29*	16	*16*	*8*	*6*	5	2	1	0	0
1:320	0	33	*38*	*19*	16	*15*	10	4	2	*4*	*4*	*4*	0	1
1:160	0	*38*	21	10	6	10	7	4	6	4	2	1	1	0
1:80	0	13	14	8	8	5	3	4	0	1	0	0	0	0
1:40	0	8	7	8	3	0	1	1	1	1	0	0	0	0
1:20	0	9	5	0	1	4	0	0	0	0	0	1	0	0
1:10	2	3	3	2	2	1	0	0	0	0	0	0	0	0
0	22	4	5	4	3	1	0	1	0	0	0	0	0	0
Total tests	24	124	131	93	87	65	52	30	21	16	9	9	1	2

Six hundred sixty-four tests on 215 children who received a total of 80 billion *H. pertussis* vaccine in three divided doses within one month. All children were from 6 to 36 months of age at time of injection.

Titers of children exposed (both those who escaped and those who were attacked) are excluded subsequent to exposure.

The median titer is in italics.

TABLE II

SUCCESSIVE AGGLUTINATIVE TITERS OBTAINED IN SEVERAL INDIVIDUALS TESTED REPEATEDLY

INTERVAL AFTER VACCINE (MO.)	E. S.	G. S.	Y. A.	D. G.	N. R.	E. F.	C. N.	R. M.	J. M.	V. S.	M. W.	C. F.	H. P.	R. H.	J. N.	A. F.	F. O.	D. W.	G. G.	F. L.
In.*															0	0	0	0	0	0
> 1											0‡	640	160	320	2,560	160	80	0	20	160
> 6									320	640	0	640	160	320	2,560		160	10	20	160
>12									80	640	0	640	160	640	1,280	2,560	640	10	80	320
>18								160	640	640		640	320	640	1,280	640	320	10	40	320
>24				640	320	320	640		80	640	0	320	80	640	640	1,280		10	80	
>30			640	640	320		640	160	160			640		640	1,280	1,280	320	40‡	80	160
>36		320		1,280			640		160	640	0	640	160	1,280		1,280	640		80	160
>42		640		640		160	1,280		160			640								
>48	160	640		640†	640	320†	1,280	320												
>54	160	640	160	1,280		320		320												
>60	320	640	80	1,280	320			320												
>66	160																			
>72	320						2,560‡													

After indoor exposures no subsequent titers are recorded.

*Titer at first injection.

†Transient outdoor "exposure" to whooping cough previous to test.

‡Whooping cough in neighborhood previous to test but no known exposure.

The largest group of children studied, 215, had received a total of 80 billion phase 1 *H. pertussis** divided into three doses and given within a period of one month (at seven- to ten-day intervals). All of the children were from 6 to 36 months of age at the time of vaccination. They were seen and bled for testing as often as possible, a few as frequently as every four months, others at longer intervals, and some only once. The tests were done over a period of four years. As the vaccine had been started two years earlier, some children were not tested during the first two years after vaccination.

Table I records the results of 664 agglutinative tests in this group. Known exposure to whooping cough, whether followed by attack or escape, removed an individual from the group. Such individual's subsequent agglutinative titers are considered in a following paper. Reinjection of *H. pertussis* vaccine likewise removed an individual from this group. It is felt, therefore, that the agglutinative titers obtained are the result of the original vaccination (plus the result of possible chance and unknown contact with *H. pertussis* and related organisms).

The persistence for six years of *H. pertussis* agglutinins in relatively high titer, median values of 1:320 to 1:640, is to be noted. Contrary to expectation, no downward trend in antibody titer was observed. Furthermore, fluctuations in the titer of the serum of given individuals were not common. Table II records successive determinations in a few of the individuals followed for two years or more. An occasional individual (as J. M. in Table II) showed variable titers, but the great majority evidenced a relatively constant antibody level graphically simulating a plateau. (A variation in titer of one dilution, up or down, is within experimental error.) An individual's level was usually reached from two to four months after vaccination.

The sera of five children never showed agglutinins (such as M. W.). One child exhibited four alternately weak positive and negative reactions. No other child reverted from positive to negative. Decreases in agglutinative titer of three dilutions or more occurred in only six instances (such as in Y. A. and J. M. in Table II). Unexplained increases in titer of three dilutions or more occurred nine times, presumably the result of unknown contact with *H. pertussis* or *B. parapertussis*. It has been shown[8] that infection with the latter organism may cause a nonspecific increase in *H. pertussis* agglutinins in vaccinated children. In two instances a temporary increase in titer followed an injection of tetanus toxoid.

This anamnestic reaction was frequently observed in 176 children in another group injected concurrently with diphtheria and tetanus toxoids and *H. pertussis* vaccine.[9] The third injection of fluid tetanus toxoid, sixteen weeks after the second, was often followed by a rise in titer of *H. pertussis* agglutinins. As in the larger group just discussed, no tendency for the agglutinative titer to decrease with time was observed.

*Vaccine kindly supplied by the Cutter Laboratories.

When vaccine was given at three to six weekly intervals rather than seven- to ten-day intervals no appreciable difference in the titers attained was observed. Four children maintained "plateaus" over 1:640 for four years.

The usual vaccine dose of 80 billion was not completed in a small number of individuals. Agglutinative reactions in these children were variable. A dose of 50 billion cells resulted in titers ranging from 1:40 to 1:640. Twenty billion cells resulted in the production of demonstrable agglutinins in only three of ten children.

H. pertussis vaccine, 80 billion cells, was given to forty-nine children over 36 months of age. Repeated tests were made. Only one failed to develop *H. pertussis* agglutinins. The antibody response was similar to that described in the younger age group, but more variation was observed between individuals. A "plateau" of agglutinins was reached in from two to four months. Median values of 1:320 were found up to three years—as long as this group has been followed. These values were slightly lower than those found in the younger age group. Nine children on repeated tests did not exhibit titers higher than 1:80. No titers, however, showed a tendency to decline with the passage of time.

Sauer[10] has advised the use of a total dose of 100 billion *H. pertussis* or more for children over 3 years of age. With this in mind twelve children were given 110 billion cells and eleven children 130 billion cells within a period of six weeks. Contrary to expectation, this increased dose of vaccine did not yield a higher distribution of titers than that found when 80 billion *H. pertussis* was used.

Periodic revaccination has been advised.[3, 11, 12] Lapin[3] noted that it was regularly followed by a rise in serum antibodies. All of twelve children reinjected by him after intimate exposure escaped whooping cough. The following observations on the effect of revaccination with 10 to 40 billion *H. pertussis* are confirmatory.

Fifty-one children were revaccinated from one to three years after the initial course (Table III). The agglutinative titers of twenty-three were known at the time of revaccination. Twenty-one of these had demonstrable agglutinins ranging from dilutions of 1:40 to 1:1280 at that time. All exhibited increases in titer thereafter. On the other hand, reinjection of the two children who had not developed agglutinins after the original vaccination led to prompt appearance of agglutinins in only one. The other produced no serum antibody after two reinjections.

As in the other groups reported, a "plateau" of agglutinins followed the reinjection. Median titers of 1:1280 were found up to two and one-half years (Table III). The number of tests done later still were too few to be significant. Little, if any, loss of agglutinins was noted, however.

These high levels differed from the median level of 1:320 found in the twenty-three older children, previously referred to, who received initial

total doses of 110 to 130 billion *H. pertussis*. Whereas the total dose of vaccine in the two groups is similar, the revaccinated younger group maintained distinctly higher levels.

TABLE III

RESULTS OF AGGLUTINATIVE TESTS AFTER REVACCINATION

TITER	AT REVACCINATION	MONTHS AFTER REVACCINATION							
		0 <6	> 6 <12	>12 <18	>18 <24	>24 <30	>30 <36	>36 <42	>42 <48
1:5120	0	1	1	0	0	0	0	0	0
1:2560	0	12	10	8	6	4	*7*	2	1
1:1280	6	*8*	*7*	*10*	6	*7*	1	0	0
1:640	6	6	8	7	6	8	0	*3*	1
1:320	4	1	2	2	5	2	0	1	2
1:160	4	0	0	0	1	0	0	1	0
1:80	0	1	0	0	0	0	0	0	0
1:40	1	0	0	0	0	0	0	0	0
1:20	0	0	0	0	0	0	0	0	0
1:10	0	0	0	0	0	0	0	0	0
0	2	1	1	0	0	0	0	0	0
Total tests	23	30	29	27	24	21	8	7	4

One hundred seventy-three tests on fifty-one children revaccinated.
Titers of children exposed are excluded subsequent to exposure.
Median titers are in italics.

DISCUSSION

In the study of the serum antibody response of pregnant women to *H. pertussis* vaccine Mishulow[13] writes "the concentration of protective, agglutinating, and complement-fixing antibodies seemed to have no direct relation to the dose of vaccine given, to the time that had elapsed since the completion of vaccination, or to the presence of these antibodies before vaccination, but depended on the person's ability to produce antibodies." The same author, however, had previously noted[14] that the agglutinin response in children was "poor" with doses of less than 70 billion *H. pertussis*. Our findings are essentially in agreement. We would emphasize, however, that doses of *H. pertussis* vaccine less than 80 billion result in lower agglutinin titers—when no alum has been added to the suspension. The addition of alum, delaying absorption, may compensate for the smaller dose as has been reported by Daughtry-Denmark[15] and Kendrick,[16] using other serologic tests.

The persistence of *H. pertussis* agglutinins, with but slight variation in titer, over a period of six years is in contrast to the frequently noted decline in both diphtheria and tetanus antitoxin concentrations after toxoid immunization. In a group of children immunized concurrently with toxoid and vaccine[9] we have observed a simultaneous persistence of antibacterial antibody and diminution in concentration of tetanus antitoxin. We know of no explanation for this diversity of persistence in circulation of these two antibodies.

The possible clinical application of these serologic studies will be discussed in Part II of this study.*

*Part II appears on p. 644 of this issue.

SUMMARY

Agglutinative reactions with *H. pertussis* were performed on the sera of 554 children who had received phase I *H. pertussis* vaccine. Two hundred and fifteen of these children were in the age groups of 6 to 36 months at the time vaccine was given. A total dose of 80 billion *H. pertussis* was given within a period of one month. Agglutinins were demonstrated in the sera of all but 5 of the 215 children. The titers attained in from two to four months after vaccination remained relatively constant thereafter. With few exceptions, no tendency for decline from a "plateau" of antibody concentration was observed up to six years after vaccination.

Agglutinative tests done on other groups of vaccinated children indicated that:

1. Prolonging the interval between the injections of vaccine had no appreciable effect on the height or persistence of agglutinins.

2. Decreasing the total dose of vaccine to 50 billion cells or lower resulted in much less constant antibody production.

3. Children over 36 months of age at the time of receiving 80 billion *H. pertussis* tended to develop slightly lower "plateaus" of agglutinins than did younger children.

4. Increasing the initial dose of vaccine in these older children did not lead to higher titers.

5. Revaccination one year or more after the initial vaccination led to increases in agglutinin titer which were thereafter maintained at high levels for at least three years.

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AN AGGLUTINATIVE REACTION FOR HEMOPHILUS PERTUSSIS

II. Its Relation to Clinical Immunity

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THE persistence of agglutinins at a relatively constant level for six years after the administration of *H. pertussis* vaccine has been described.[1] The following observations were made with a desire to determine the clinical significance of this immunologic response. The possibility that the agglutinative reaction might be an index of immunity was subject to proof—only, however, by prolonged observation of large numbers of individuals.

Over five hundred infants and children have been followed in the clinic as closely as possible, some for as long as five years. Obviously, many individuals have been lost from the group and new members have been added monthly. Exposures have been noted and agglutinative reactions repeated every four to six months when possible.

Exposure, for the purpose of this study, was defined as indoor contact with a child in the first three weeks of clinical whooping cough. The duration of the contact was required to be at least one hour unless the coughing child was seen to cough directly into the vaccinated child's face. In six instances this occurred. In the remainder, where contact was for one hour or more, the sick child must have been heard or seen to cough during the period of time. The diagnosis of whooping cough in the contact was required to have been made by a physician. With these criteria the communicability rate for unvaccinated children had previously been found to be 90.6 per cent.[2]

Outdoor "exposures," even though bacteriologically proved, were excluded when followed by escape. It was felt that such contacts would be inadequate tests of immunity. Outdoor exposures when followed by attacks of pertussis were, however, obviously valid and were included as exposures. Two additional cases occurred without known exposure. They are included as exposures as well as cases.

A total of seventy-nine exposures were observed, twenty-four of which were familial (Table I). In twenty instances the exposures were proved bacteriologically by nasopharyngeal swabs[3, 4] or by cough plates. In eight additional instances the diagnosis in the coughing child was verified by the characteristic lymphocytosis and in sixteen others, by the agglutinative reaction already referred to. Agglutinins in the serum of the

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TABLE I

CLASSIFICATION OF EXPOSURES RESULTING IN

	ESCAPES		CASES	
	FAMILIAL EXPOSURES	INDOOR (NONFAMILEAL) EXPOSURES	FAMILIAL EXPOSURES	OTHER EXPOSURES
Bacteriologically proved	13	5	1	1 (Outdoor)
Hematologically verified by lymphocytosis	1	7		
Serologically substantiated by agglutinative reaction	3	5	5	3 (1 Outdoor) (2 Unknown)
Clinically diagnosed only	1	34		
Total	18	51	6	4

Outdoor "exposures" resulting in escape are disregarded.
All cases are included regardless of type of exposure.

coughing child (the "exposer") or a rise in titer of three tubes or more in the exposed child was considered serologic substantiation of the exposure (Table I).

In fifty-three instances exposures occurred within six months subsequent to a determination of the agglutinative titer. In the remaining twenty-six exposures the interval between the test and exposure was from seven to eighteen months. In view of the relative constancy of agglutinative titer with passage of time,[1] it is felt that this long interval does not invalidate the observations.

The majority of the exposed children had received phase I *H. pertussis* vaccine in a dose of 80 billion cells. Eight children had received less than this dose. Nine had received more (three initially and six because of revaccination). Seven children received the vaccine concurrently with fluid diphtheria and tetanus toxoids, and five children received the vaccine concurrently with alum-precipitated diphtheria and tetanus toxoids.[5] Two children received "pertussis antigen (detoxified)." (Both subsequently developed whooping cough.)

The interval between completion of injections of vaccine and exposure varied from fifty-one days to fifty-nine months.* Four children were exposed two times, escaping each time. Table II shows that most of the

TABLE II

INTERVAL BETWEEN COMPLETION OF VACCINE AND EXPOSURE

	51 DAYS TO 1 YEAR	1 TO 2 YEARS	2 TO 3 YEARS	3 TO 4 YEARS	4 YEARS TO 59 MONTHS	TOTAL
Escapes	21	24	16	4	4	69
Cases	5*	4	1	0	0	10

*Two of these cases had received "pertussis antigen (detoxified)."

*In the six intances where revaccination was performed, the interval taken is from the date of revaccination to exposure. Instances in which revaccination was performed shortly after exposure (during incubation period) have been excluded.

exposures (and all of the cases) occurred within a three-year interval after vaccination. This is principally due to the great difficulty in following a large group of children over a period of years in a community where residence is changed frequently. It is apparent, however, that no progressive loss of immunity with the passage of time was observed in this group.

Ten cases of whooping cough were observed. In nine the titer was known before the attack and in the tenth a titer of "0" was found on the twelfth day of the incubation period. It is therefore assumed that the titer at the time of exposure was "0." Six cases resulted from indoor exposures as defined above. Two followed outdoor exposures and two occurred without known exposure. The cases will be described in detail later.

The agglutinative titer before exposure (and before the two attacks where exposure was unknown) is shown in Table III. Escapes occurred

TABLE III

THE TITER BEFORE EXPOSURES IN RESULTING ESCAPES AND CASES

TITER	ESCAPES FROM				CASES
	FAMILIAL EXPOSURES	BACTERIOLOGICALLY OR HEMATOLOGICALLY OR SEROLOGICALLY SUBSTANTIATED HOUSEHOLD EXPOSURES	CLINICALLY DIAGNOSED (ONLY) HOUSEHOLD EXPOSURES	ALL TYPES OF PRECEDING EXPOSURES (TOTAL)	
1:2560		1	2	3	
1:1280	3	1	5	9	
1:640	3	3	10	16	
1:320	5	6	7	18	
1:160	4	1	4	9	3
1:80	2	4	2	8	1
1:40			1	1	1
1:20	1		1	2	1
1:10					
Negative		1	2	3	4*
Total number	18	17	34	69	10

*In one of these cases the titer was obtained twelve days after exposure. Being negative at that time presumably it was negative before exposure.

in three individuals having no agglutinins and in sixty-six individuals with titers ranging from 1:20 to 1:2560. Forty-six, or two-thirds, of the escapes occurred, however, in children with titers of 1:320 or higher. On the other hand, the cases occurred in individuals with titers of 1:160 and lower. Four of the ten had had no agglutinins. The difference in the distribution of pre-exposure titers in the sixty-nine escapes as compared to that in the ten cases is obviously significant. It would therefore appear that in vaccinated children immunity may exist in the absence of demonstrable circulating antibody. Susceptibility, on the other hand, does not appear to be associated with the carriage of agglutinins in titers of 1:320 or over (with the technique used).

The histories of the eight children who were exposed and escaped three years or more after completion of vaccine are summarized in Table IV. Two had received less than the usual dose of 80 billion *H. pertussis*. Their pre-exposure agglutinative titers varied from 1:80 to 1:1280.

TABLE IV

HISTORIES OF CHILDREN WHO ESCAPED FOLLOWING EXPOSURE THREE YEARS TO FIFTY-NINE MONTHS AFTER COMPLETION OF VACCINE

NAME	SEX	VACCINE DOSAGE (BILLIONS)	INTERVAL BETWEEN VACCINE AND EXPOSURE	INTERVAL BETWEEN LAST PREVIOUS AGGLUTINATION TEST AND EXPOSURE	TYPE OF INDOOR EXPOSURE	TITER BEFORE EXPOSURE	TITER AFTER INCUBATION PERIOD
G. T.	M	80	40 mo.	3 mo.	C.D.O.	80	80
D. M.	F	80	42 mo.	3 mo.	C.D.O.	1,280	1,280
J. M.	M	80	43 mo.	7 mo.	C.D.O.	160	40
L. M.	M	80	45 mo.	6 days	Fam. B+	1,280	N.D.
A. H.	M	80	49 mo.	10 mo.	C.D.O.	640	1,280
J. W.	M	80	49 mo.	12 mo.	S.S.	160	320
B. W.	M	50	54 mo.	3 mo.	S.S.	80	1,280
R. G.	M	50	59 mo.	16 mo.	Fam. S.S.	320	1,280

Fam., familial.
C.D.O., clinically diagnosed only.
B+, bacteriologically proved.
S.S., serologically substantiated (see text).
N.D., not done.

The histories of the ten children who were attacked with whooping cough are summarized in Table V. Four cases only were typical, the remainder were mild or atypical (clinically not whooping cough). From two mild and one atypical case *H. pertussis* was isolated. The diagnosis in the remaining seven rests on the clinical and serologic evidence. The possibility that a few of these may have been parapertussis cannot be excluded on serologic evidence, as a nonspecific rise in *H. pertussis* agglutinins may occur when vaccinated children are attacked with parapertussis.[6] However, as *Bacillus parapertussis* is isolated with greater ease than *H. pertussis*, in the four instances recorded as "bacteriologically negative" the possibility of the attack being due to *B. parapertussis* seems to be slight. In the remaining three cases (R. D., M. W., and B. W.) the attack was described to us as typical whooping cough in the patient or sibling. As parapertussis infections are usually mild, we have felt that the evidence was in favor of pertussis.

It will be noted in Table V that three of the four typical attacks of whooping cough occurred in children (D. K., M. W., and B. W.) who had received only 20 billion *H. pertussis* or "pertussis antigen." These children were 3 years of age or older at the time of injection.

The rise in agglutinin titer in vaccinated children during an attack, shown in Table V, directed inquiry to the effect of exposure on the titers of those children who escaped. A comparison was made between the pre-

TABLE V

SUMMARY OF HISTORY OF CASES OF PERTUSSIS

NAME	SEX	VACCINE DOSAGE (BILLIONS)	AGE AT VACCINATION	INTERVAL BETWEEN VACCINE AND EXPOSURE	INTERVAL BETWEEN LAST PREVIOUS AGG. TEST AND EXPOSURE	TITER BEFORE EXPOSURE	TITER DURING INCUBATION PERIOD*	TITER DURING ATTACK	TITER LATER	TYPE OF CASE
B. P.	F	80	5 yr.	16 mo.	11 mo.	20		2,560		Mild, B+
E. P.	F	80	7 mo.	30 mo.	12 mo.	160		80, 2nd day 2560, 18th day		Mild, B+
N. Mc.	M	80	7 mo.	10 mo.	7 days	80		80, 4th day 2,560, 55th day		Typical B-, S.S.
R. T.	F	80	13 mo.	21 mo.	15 mo.	160	640	640	640	Atypical B+ (Duration, twelve days)
R. D.	F	80	9 yr.	3 mo.	2 mo.	0			1,280	Mild, no B, S.S. (Brother had typical attack)
L. M.	M	80	3 yr.	5 mo.	2 mo.	160			1,280	Mild, B-, S.S. (Duration, seven days)
D. K.	F	20	5 yr.	18 mo.	14 mo.	40		1,280	2,560	Typical B-, S.S.
P. K.	M	20	18 mo.	13 mo.			0		160	Mild, B-, S.S. (Duration, twelve days)
M. W.	F	Pertussis antigen 6 c.c.	4 yr.	2 mo.	2 weeks	0			160	Typical, no B, S.S.
B. W.	M	Pertussis antigen 6 c.c.	3 yr.	2 mo.	2 weeks	0			160	Typical, no B, S.S.

*Incubation period arbitrarily taken as 2 weeks (see reference [7]).
B+, bacteriologically positive.
B-, bacteriologically negative.
No B, no bacteriological test done.
S.S., serologically substantiated.

exposure titers and the titers obtained during the possible incubation period (arbitrarily chosen to be two weeks.[7]) A variation in titer of one tube was considered within experimental error. During the possible incubation period, the sera of twenty-seven children remained constant or showed only one tube variation. The sera of five children showed increases in titer of two tubes or more. A girl with repeatedly negative agglutinative reactions before exposure developed agglutinins in a titer of 1:320 eleven days after the termination of a three-week daily exposure. To these five escapes may be added the case of R. T., in whom an increase in titer occurred during the incubation period (Table V). In only one instance was the titer during the possible incubation period found significantly lower than previously. This exposure had been bacteriologically proved.

In sixty instances it was possible to compare the pre-exposure agglutinative titers with those obtained later than the possible incubation period. Here a higher proportion of increases in titer might be expected. However, in forty-six children no significant variation in titer (more than one tube) occurred. In twelve instances increases of from two to six tubes were observed, and in two instances decreases of two tubes occurred. (These last two sera were obtained three months after termination of exposure.)

DISCUSSION

From a critical, if not from a clinical, point of view it is regretted that more cases of pertussis were not observed. Further observations might have yielded a case developing in an individual with high agglutinative titer. The fact that so few cases were encountered indicates the efficacy of the vaccine used. (The inefficacy of a soluble antigen used only twice but with unfortunate results is also evident.)

Indirect evidence in support of the conclusion that susceptibility to pertussis is not associated with the carriage of agglutinins in moderately high titer may be found in the following observations on unvaccinated children. Agglutinative tests done during the first two weeks of attacks of pertussis in twenty-three children were negative in twenty-one children. Titers of 1:20 and 1:320 were found in the other two. It is therefore a warranted assumption that the great majority of unvaccinated children who were attacked had no agglutinins at the time of their exposure. This was further substantiated by finding agglutinins in the sera of only 10 of 101 infants and children with negative histories.[8] Two of the infants with no agglutinins in this group of 101 have since had bacteriologically proved attacks.

In our opinion these and the preceding observations[1] may be applied to the clinical problem of pertussis immunization in the following manner. The initiation and maintenance of a high titer of serum antibody against *H. pertussis* are desirable. In the age group under 3 years of age, and

with vaccine to which alum has not been added, 80 billion *H. pertussis* usually initiates and maintains a "plateau" of agglutinins at which susceptibility is not observed. Revaccination with a fractional dose one to two years later results in increases in titer in all those able to produce serum antibody but not in the rare individual incapable of reacting serologically. Further repeated revaccination is apparently unnecessary.

The agglutinative reaction has a limited clinical value as a test of immunity. Quantitative tests are essential. The amount of agglutinins is as important as their presence. It is believed that a test performed two to three months after vaccination indicates the amount of agglutinin an individual may be expected to carry for five years. High titers indicate successful immunization. Low titers or negative tests on the other hand do not indicate susceptibility. Those individuals with titers of 1:10 to 1:160, being known to have the capacity of manufacturing antibodies, might reasonably be given an additional injection of vaccine after an interval of a few months. A rise in titer could then be expected. Individuals showing no agglutinins after vaccination, on the other hand, may not be able to synthesize serum antibody. Reinjection may have no demonstrable effect. Some of these rare individuals may nevertheless be immune.

SUMMARY

The relationship between clinical immunity and the agglutinin titer in children given *H. pertussis* vaccines was studied over a period of four years. Periodic tests in a group of 554 children were made.

Seventy-nine indoor exposures, twenty-four of which were familial, occurred. Ten cases of pertussis (six from familial exposures) resulted. Among the sixty-nine individuals who escaped, the last agglutinative titer prior to exposure varied from 0 to 1:2560. Forty-six had titers of 1:320 or higher. Among the ten individuals who were attacked with pertussis, the pre-exposure titers varied from 0 to 1:160. These observations suggest that whereas immunity may exist in the absence of demonstrable agglutinins, susceptibility does not occur in the presence of agglutinins in high titer.

The clinical application of these findings is discussed.

ADDENDUM

Since going to press two more escapes and two more cases have occurred.

A girl, who received vaccine eight months previously and had an agglutinin titer of 1:160 six months previously, escaped following a clinically diagnosed indoor exposure.

A girl, who received vaccine forty-six months previously and had an agglutinin titer of 1:1280 eleven months previously, escaped following a hematologically substantiated familial exposure.

A girl, who received vaccine forty-four months previously and had an agglutinin titer of 1:40 nine months previously, had typical bacteriologically proved pertussis following an unknown exposure. A rise in agglutinin titer to 1:1280 was observed.

A boy, who received vaccine fifty-two months previously and had an agglutinin titer of 1:40 six months previously, suffered mild bacteriologically proved pertussis following an indoor exposure of two weeks' duration.

These observations are quite in accord with those reported above.

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THE CHEMOTHERAPY OF INFANTILE DIARRHEA: A COMPARISON OF SULFADIAZINE AND SULFAPYRAZINE

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DURHAM, N. C.

AS STATED in previous papers,[1, 2] the treatment of infantile diarrhea in the Pediatric Department of the Duke Hospital has become somewhat standardized since the advent of the sulfonamides. The same general plan of treatment* has been used for the last few years. The only change from one year to another has been the attempt to find the most efficacious sulfonamide. To this end, Taylor in 1940 found that sulfathiazole worked very well in all types of diarrhea.[1] The author in 1941 compared sulfathiazole and sulfaguanidine in alternate cases of infantile diarrhea and found that although both sulfonamides were satisfactory, sulfathiazole seemed to be more effective in the parenteral diarrheas.[2]

Alternate diarrheal patients in 1942 were given sulfadiazine and sulfapyrazine† (Tables I and II). Fifteen of these patients were treated with sulfadiazine and twenty-two with sulfapyrazine from the day of admission till all symptoms and signs of infection had ceased (Table III). The dosage was the same for both drugs; i.e., 0.1 Gm. per kilogram of body weight per twenty-four hours, each patient receiving one-half of his initial twenty-four-hour dose immediately and then the rest of the dose every four hours.

The blood and urine of the patients receiving sulfapyrazine were examined daily, and those of the sulfadiazine group, every other day. The average blood level of sulfapyrazine was from 1 to 3 mg. per cent. Microscopic hematuria was observed in three patients receiving sulfadiazine but in none in the sulfapyrazine group. No drug rash or other toxic signs were observed in either group.

Clinically, fourteen of the thirty-seven infants had bacillary dysentery and twenty-three had parenteral diarrhea; i.e., they had infection elsewhere, usually of the upper respiratory tract. Three of the infants with clinical bacillary dysentery had Flexner Y bacilli in their stools, and one

*The routine basic treatment which all diarrheal patients received was as follows: (1) one-sixth molar sodium lactate as indicated by the admission carbon dioxide combining power, one-half the dose being given intravenously and one-half subcutaneously; (2) nothing by mouth for the first twenty-four hours except Ringer's solution and weak tea as desired; (3) after twenty-four hours, equal parts of evaporated milk and water with 0.75 per cent lactic acid and 5 per cent Casec were offered in amounts furnishing 20 calories per kilogram of body weight; if this was taken, the quantity was increased by 20 calories per kilogram every second day until the caloric requirements were attained; (4) 5 per cent dextrose intravenously and other parenteral fluids as indicated by the degree of dehydration up to 30 c.c. per kilogram of body weight in twenty-four hours; (5) blood transfusions following hydration, if indicated; (6) daily maintenance oral doses of thiamine chloride and ascorbic acid.

†Sulfapyrazine (2-sulfanilamidopyrazine) is an isomer of sulfadiazine and was synthesized by Ellingson in 1941.[3] In experimental pneumococcal infections, sulfapyrazine is one of the most effective, if not the most effective, of the sulfonamides.[4] At Sydenham Hospital in Baltimore its use in the treatment of meningococcic meningitis has been very satisfactory.[5] Thanks are due Mead Johnson & Co. for supplying the sulfapyrazine.

had Flexner V bacilli. In none of the other patients' stools were any pathogenic bacteria found, although they were cultured daily for three days after admission.

TABLE I

FIFTEEN PATIENTS TREATED WITH SULFADIAZINE

SEX	RACE	AGE (MO.)	CLINICAL DIAGNOSIS	DAILY NUMBER OF STOOLS PRIOR TO ADMISSION	DEGREE OF DEHYDRATION	SULFADIAZINE (GM.)			DAYS UNTIL CURE
						ADMISSION DOSE	Q.4 H. DOSE	TOTAL DOSE	
M	C	2	P.D.	5 to 7 (5 days)	Marked	0.25	0.1	3.85	3
M	C	15	Dys.	Many (1 day)	Marked	0.3	0.1	4.5	4
F	W	3	P.D.	6 to 8 (2 weeks)	Marked	0.25	0.1	3.25	4
M	W	12	Dys.	10 to 12 (2 weeks)	Marked	0.25	0.15	7.45	6
M	C	11	P.D.	Many (5 days)	Marked	0.5	0.15	5.0	4
M	C	3	P.D.	12 to 16 (7 days)	Marked	0.25	0.15	4.75	4
M	W	2	P.D.	4 to 10 (7 days)	Marked	0.15	0.1	3.15	5
M	C	2	P.D.	Many (2 weeks)	Marked	0.3	0.15	6.6	4
F	C	3	P.D.	5 to 7 (5 days)	Moderate	0.2	0.2	6.2	3
F	C	6	P.D.	8 (3 days)	Moderate	0.5	0.15	5.0	3
F	C	10	Dys.	12 (9 days)	Moderate	0.5	0.25	6.25	3
M	C	24	Dys.	6 to 7 (2 days)	Moderate	0.75	0.25	5.25	3
M	C	36	Dys.	10 (10 days)	Slight	1.0	0.3	8.2	3
M	W	2	P.D.	6 to 9 (7 days)	Slight	0.3	0.1	2.1	4
M	W	6	Dys.	5 to 7 (2 weeks)	Slight	0.5	0.15	6.8	6

TABLE II

TWENTY-TWO PATIENTS TREATED WITH SULFAPYRAZINE

SEX	RACE	AGE (MO.)	CLINICAL DIAGNOSIS	DAILY NUMBER OF STOOLS PRIOR TO ADMISSION	DEGREE OF DEHYDRATION	SULFAPYRAZINE (GM.)			DAYS UNTIL CURE
						ADMISSION DOSE	Q.4 H. DOSE	TOTAL DOSE	
F	W	6	P.D.	15 to 20 (3 weeks)	Marked	0.25	0.15	6.55	4
M	W	5	Dys.	5 to 6 (7 days)	Marked	0.25	0.1	5.05	3
F	W	5	P.D.	4 to 5 (2 weeks)	Marked	0.25	0.1	2.65	3
M	W	6	P.D.	5 to 7 (3 days)	Marked	0.3	0.1	2.7	3
M	W	1.25	P.D.	5 to 6 (5 days)	Marked	0.4	0.1	1.3	4
M	W	2.5	P.D.	6 to 10 (4 weeks)	Marked	0.25	0.1	2.65	3
F	W	0.5	P.D.	8 to 10 (2 weeks)	Marked	0.25	0.1	2.65	4
M	W	3	Dys.	Many (5 days)	Marked	0.25	0.1	3.25	4
F	W	7	P.D.	Many (3 days)	Moderate	0.25	0.15	4.75	3
M	C	11	P.D.	6 to 7 (2 days)	Moderate	0.25	0.25	3.25	3
M	C	10	Dys.	Many (5 days)	Moderate	0.25	0.1	3.85	4
F	W	3	Dys.	15 to 30 (7 days)	Moderate	0.5	0.1	3.5	4
M	C	6	P.D.	10 to 12 (3 days)	Slight	0.25	0.15	3.85	3
F	W	11.5	Dys.	10 to 15 (3 days)	Slight	0.5	0.25	8.0	4
F	C	13	Dys.	15 (2 days)	Slight	0.25	0.25	3.25	3
M	W	3	P.D.	15 (4 days)	Slight	0.3	0.1	3.3	2
M	C	19	P.D.	5 to 7 (2 days)	Slight	0.5	0.25	3.5	2
F	W	5	P.D.	10 to 17 (5 weeks)	Slight	0.25	0.15	3.85	4
M	C	3	Dys.	12 (1 week)	Slight	0.5	0.25	6.5	4
F	C	3	P.D.	Many (2 weeks)	Slight	0.5	0.25	3.5	3
M	C	10	P.D.	12 to 15 (2 weeks)	Slight	0.5	0.25	3.5	3
M	C	19	Dys.	10 to 15 (7 days)	Slight	0.5	0.25	3.5	3

TABLE III

TOTAL PATIENTS TREATED ACCORDING TO TYPE OF DIARRHEA

	TOTAL NUMBER OF PATIENTS	TREATED WITH SULFADIAZINE		TREATED WITH SULFAPYRAZINE	
		NUMBER OF PATIENTS	AVERAGE DAYS TO CURE	NUMBER OF PATIENTS	AVERAGE DAYS TO CURE
Parenteral diarrhea	23	9	3.7	14	3.1
Bacillary dysentery	14	6	4.1	8	3.6

TABLE IV

DISTRIBUTION OF PATIENTS ACCORDING TO DEGREE OF DEHYDRATION

DEHYDRATION	TREATED WITH SULFADIAZINE		TREATED WITH SULFAPYRAZINE	
	NUMBER OF PATIENTS	AVERAGE DAYS TO CURE	NUMBER OF PATIENTS	AVERAGE DAYS TO CURE
Marked	8	4.2	8	3.5
Moderate	4	3.0	4	3.5
Slight	3	4.3	10	3.1
Results	15	3.8	22	3.3

Six of the clinical bacillary dysentery groups were given sulfadiazine and eight received sulfapyrazine. Of the parenteral diarrhea series, nine were treated with sulfadiazine and fourteen with sulfapyrazine. Both the drugs were equally effective in both the dysentery and parenteral diarrhea cases. In no instance was it necessary to change from one sulfonamide to the other.

Analyzing the cases according to degree of dehydration revealed that both sulfonamides were equally effective in all three groups (Table IV).

CONCLUSION

Sulfadiazine and sulfapyrazine, in the doses used, were equally effective in the treatment of clinical bacillary dysentery and parenteral diarrhea. Sulfapyrazine did not produce any toxic reactions in this series of twenty-two patients.

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A NEW APPROACH TO THE QUANTITATIVE ANALYSIS OF CHILDREN'S POSTURE

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VARIOUS methods of appraising posture have been recommended: Posture as a whole has been rated. Raters either used standards* (such as the popular ones of the Children's Bureau) or relied on the validity of their own judgment as to what constitutes desirable posture.[2] Certain body regions have been appraised separately.[3] Frequently a certain type of posture has been described as "ideal" and deviations were rated rather arbitrarily as "moderate," "severe," etc.; that is, only one point of the rating scale was defined by adequate cues. Certain proportions, angles, etc., have been measured both on living subjects and on photographs.[2, 3, 4] Finally such regional measurements have been compared with subjective ratings of the above-mentioned types in order to arrive at more objective measures of posture as a whole.[2, 4]

All these methods have been useful for certain purposes, but all of them have definite limitations. There still is a need for quantitative, well-defined measures which can be easily applied.

We feel that there is as yet no sound theoretical basis for rating posture as a whole. In practice it involves arbitrary decisions as, for instance, weighing excessive lumbar lordosis in one child against round shoulders or pronated feet in another one. These difficulties are minimized if limited body regions are studied separately.

For research purposes the appraisal of photographs offers advantages over the study of the living child. The value of permanent records is obvious. Also, photographs lend themselves better to measurements. One should remember, however, that posture changes constantly and that the photograph preserves only a single phase of a moving picture. Meticulous measurements with millimeter rule and protractor are possible but beyond a certain point accuracy does not add to the validity of measurements.

OUR METHOD

We have constructed rating scales for some regional posture variables with photographs illustrating the scale points. The need for verbal cues (see below) is almost eliminated. This method of rating is more objective than the above-mentioned ones; it avoids labeling variations as good or bad; it is a quantitative method but far less time-consuming than measurements.

From the Samuel S. Fels Research Institute, Antioch College.

*Only a few references are quoted. A comprehensive review of the voluminous literature seemed beyond the scope of this communication.

MATERIAL

At the Samuel S. Fels Research Institute approximately 170 presumably normal, healthy white children are seen at regular intervals. Nude photographs are taken every six months. Front, side, and rear views are photographed in natural (not optimal!), symmetric, erect posture. For the profile view the child is sometimes asked to move the arms slightly forward so that the back curves are better seen. For the rear views the feet are pointed straight forward so that their axes are parallel. Ankles and/or knees should touch. The natural position of legs and feet is seen in the front views.

We have analyzed approximately 1,000 lateral and 400 rear view photographs of children between the ages of 2 and 12 years. Posture of children under 2 years of age involves many special problems peculiar to that age period and will not be considered here.

CONSTRUCTION OF THE SCALES

We selected at random fifty photographs and ranked them according to the severity of a certain defect;* let us say knock-knees. We then selected a few of these pictures as standards and used them to rate another group of fifty pictures. The original standards were gradually replaced by new ones whenever it seemed necessary. Finally all pictures were rated on our last standards (Figs. 1 to 5).

The scales may be extended in both directions whenever the material to be rated requires it. The present standards represent the range of the variations found in our group, but we know that more extreme cases are found in the general population since our sample is not very large and contains only normal children.

No effort was made to use the same number of standard photographs for each scale. The number of standards was chosen according to the smallest difference which could be seen with relative ease. More experienced raters can often make finer distinctions. The number of scale points is not limited by the number of standards.

THE SCALES AND THEIR USE

1. *Knock-Knees* (Fig. 1).—The scale is easy to use if feet and legs are in standard position.

2. *Pronation of Feet* (Fig. 2).—One should look for curving of the Achilles tendon, tilting of the heel, the relative position of the external and internal malleolus, and the medial protrusion of the talus and navicular. Caution should be used if lateral bowing of the tibias is present, because in that condition the relative position of leg and foot are similar and the Achilles tendon will show some curving. Pronation in very small children is more difficult to rate, because the bony contours are often obscured by fat pads. Standard position is essential. The

*The terms "defect" and "variable" are used here interchangeably. No arbitrary line was drawn between "normal" and "abnormal."

feet must be parallel since external rotation of the legs (toeing out) pronates the feet. The internal malleoli should barely touch; they should not be pressed against each other and so act as a supporting brace for the lower foot joint.

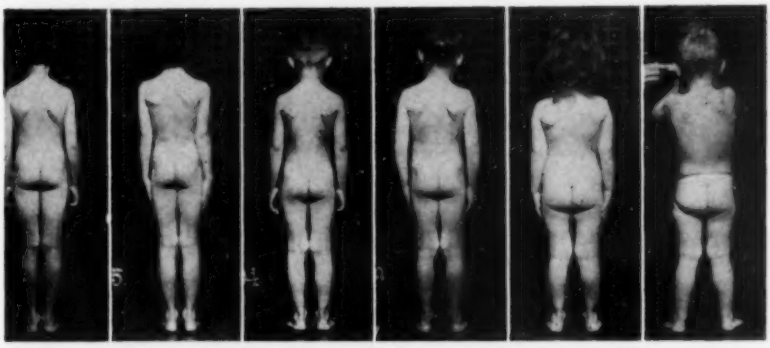

Fig. 1.—Standards for rating knock-knees: *1* shows absence of knock-knees; *6* represents the most marked group of knock-knees found in our children. The children shown here differ considerably in age and height. The photographs were enlarged in such a manner as to make their heights appear equal.

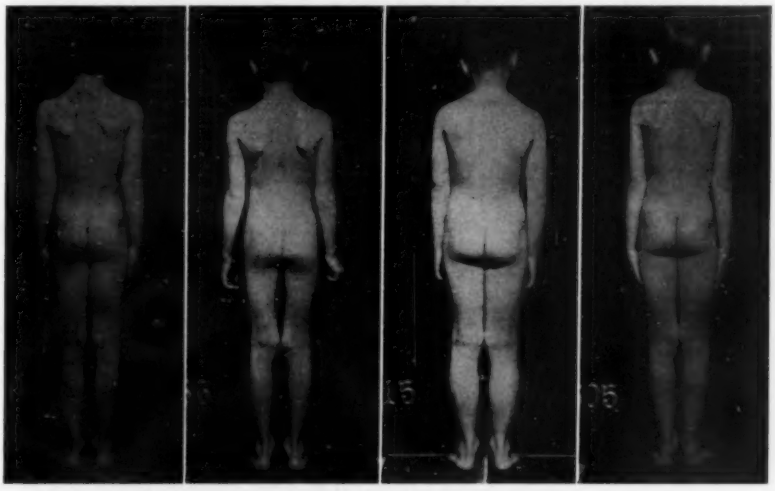

Fig. 2.—Standards for rating pronation of feet: *1* shows absence of pronation, *4* represents the most marked group.

3. *Hyperextended Knees* (Fig. 3).—This must not be confused with backward bowing of the tibias, though we found these conditions sometimes associated.

4. *Lumbar Lordosis* (Fig. 4).—Lordosis is fairly easy to rate even if part of the back is obscured by the arms. It becomes more difficult and

somewhat arbitrary in the rare cases in which the lumbar region shows rather acute angulation instead of the usual wide arc. Prominent buttocks due to fat and/or muscular development seem to accentuate the lumbar curve and may cause faulty ratings.

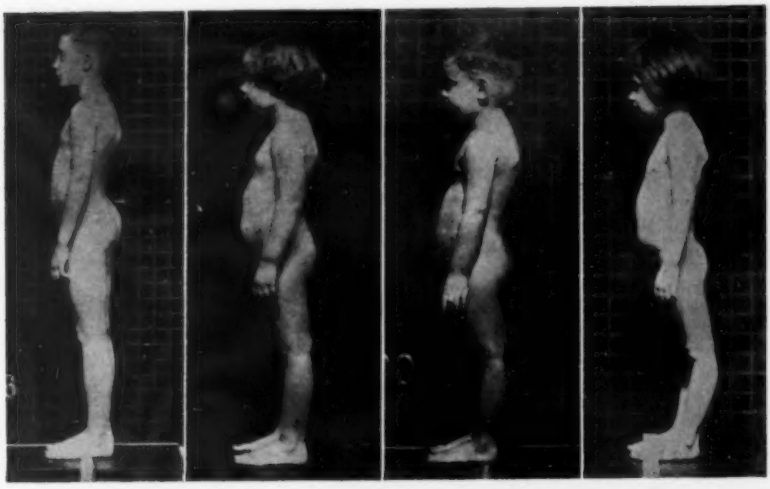

Fig. 3.—Standards for rating hyperextended knees. Explanation as in Figs. 1 and 2.

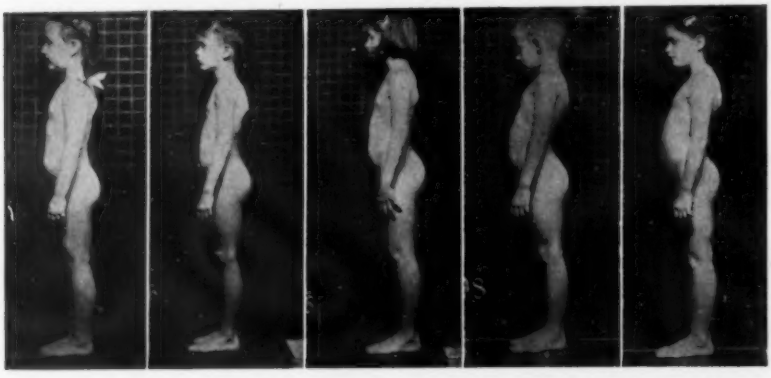

Fig. 4.—Standards for rating lumbar lordosis: *1* does not represent absence but the slightest degree of lumbar lordosis found.

5. *"Slumped Back"* (Fig. 5).—We have used this term for a combination of signs commonly seen in preschool children, less frequently later. The main feature is a relaxation of the upper trunk. There is mild or moderate kyphosis of the thoracic and cervical spine. Head and shoulders drop forward; the chest appears flat, the anterior body

contour shows a "kink" in the region of the xiphoid. The distance between chest and pelvis is shortened, the abdominal muscles relax, and the abdomen consequently protrudes.

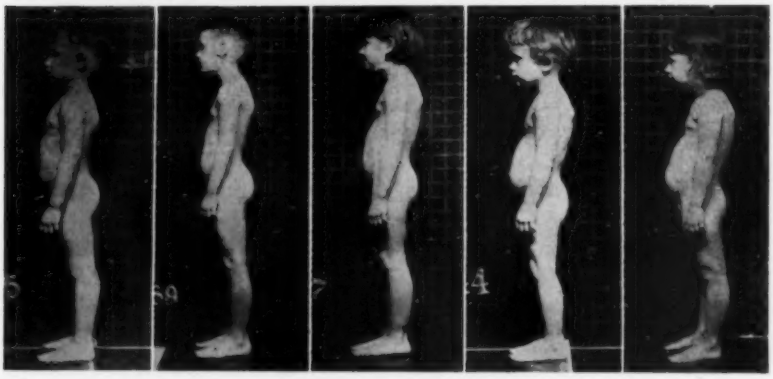

Fig. 5.—Standards for rating "slumped back." Explanations as in Figs. 1 to 3.

Difficulty in rating is caused by the fact that the appearance of this condition changes distinctly with age. In small children almost the entire back is involved. The convexity of the spine may reach down to the lumbar region. In older children the slump is usually limited to the upper thoracic and lower cervical region. We suspect that this slump is a precursor of some rigid round backs of adults. The scale should not be used past the age of 10 years. It seemed most valuable between the ages of 3 and 6 years.

These are the only scales which we have used. Many others can undoubtedly be constructed and used to advantage.

We have rated only photographs. The scales could, however, be used on the living child if lack of time or funds precludes the use of photographs (public schools, camps, surveys of various types).

RELIABILITY

All photographs were at first rated independently by two of us (M. R. and V. L.). But in the process of establishing the scales it became necessary to compare ratings, discuss discrepancies, and make some revisions of our ratings. The final ratings agreed very well but cannot be considered independent. We therefore used fifty additional photographs for the study of reliability. Ratings were made independently by the two of us (A and B) and a third examiner, a psychologist (C), who had neither previous experience in this field nor previous acquaintance with the scales. Ratings on the five variables were intercorrelated (Table I).

Let us examine these coefficients: A and B agreed exceedingly well on knock-knees and lumbar lordosis, less closely but still well on the re-

TABLE I

	KNOCK-KNEES	PRONATION	HYPER-EXTENDED KNEES	LUMBAR LORDOSIS	SLUMPED BACK
$r_{A, B}$	0.94	0.77	0.79	0.91	0.75
$r_{A, C}$	0.93	0.80	0.69	0.74	0.39
$r_{B, C}$	0.95	0.76	0.68	0.78	0.53

maining variables. C agreed with A and B as well as they among themselves on knock-knees and pronation but differed more on the three other variables. The poor agreement on slumped back could be explained by the previously mentioned difficulties involved in the use of this scale.

A high correlation coefficient does not necessarily imply that the ratings are nearly identical. A high coefficient could be obtained if observer A would consistently rate one scale point higher than observer B. We calculated therefore the mean differences between the ratings of A and B. They were exceedingly small, ranging from 0.24 scale points for lumbar lordosis to 0.06 points for pronation.

We also correlated ratings on fifty pairs of photographs taken six months apart. The coefficients given in Table II were obtained.

TABLE II

Knock-knees	0.85
Pronation	0.85
Lordosis	0.66
Slumped back	0.66
Hyperextended knees	0.55

The comparatively low correlations for lumbar lordosis, slumped back, and hyperextended knees suggest that these variables are more susceptible to random changes. In these variables developmental changes are likely to be obscured by instantaneous postural changes, such as those changes which occur from moment to moment due to effort, fatigue, balance, etc. Changes in knock-knees and pronation ratings may, therefore, be considered better measures of individual progress. Changes in the other variables are less valuable for the study of individual than for group studies.

AGE TRENDS AND "NORMAL" POSTURE

"Normal" has two meanings: (1) average or some other measure of central tendency and (2) free of defects. The first is a biometric, the second a medical definition. The averages of our five posture variables and their changes with age are shown in Fig. 6. It is evident that the averages at certain ages deviate considerably from what is commonly considered good posture. The average normal child has considerable knock-knees at 3 years of age, and the average lumbar lordosis at 10 years is more marked than is usually considered desirable. But there

are good reasons for calling knock-knees, hyperextended knees, pronated feet, marked lumbar lordosis, and slumped back defects. They offend our esthetic sense, and they are mechanically inefficient. One would expect all these defects to become worse (stretching of certain muscles and ligaments and shortening of their antagonists). Surprisingly enough, most of these conditions improve with age.[2, 3, 4, 5] Lumbar lordosis becomes more marked throughout the age range studied here but decreases during adolescence.[2, 3, 4] Only pronation remained nearly constant in our group.* These "defects" may be considered an "ugly duckling" stage. From the point of normality they are perhaps comparable to the "physiologic" anemia of infants which is considered a normal though undesirable phenomenon.

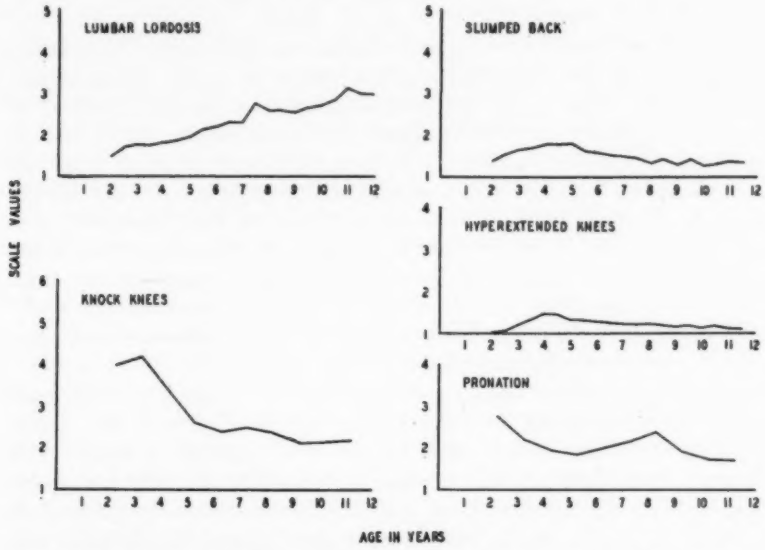

Fig. 6.—Age trends of the posture variables: Ordinates = scale points; abscissae = age in years. The curves represent the mean values of our ratings on the entire group of children studied.

We have examined the frequency distributions of our variables at various age levels. Knock-knees during the preschool period and lumbar lordosis throughout approximated normal distributions. All other variables showed more or less skewed distributions. This was particularly true for hyperextended knees. Most children never showed any hyperextension. In these cases the medians are more suitable measures of central tendency and normal posture than the above shown means (Fig. 6). This is another reason for calling the following

*According to Sweet[5] pronation decreases considerably with age. This disagreement may be due to the following: Small children are very frequently toeing out and consequently walk with pronated feet. In many cases this pronation disappears if the children assume the standard posture (feet parallel) from which our ratings were made.

conditions defects: hyperextended knees, slumped back, all but very mild knock-knees after the preschool period, or very mild pronation at any age.

A relatively heavy child has more weight to balance and may be expected to show more severe knock-knees. We have correlated knock-knee ratings with weight: length ratios at various age levels. The correlation was high at 3 years, 0.61, dropped gradually to insignificance at 6 years, –0.12, and rose again to reach 0.69 at 10 years. The low correlation at 6 years is probably due to the fact that both weight and knock-knees show little variability at that age. No sex differences were found at any age. Rickets could not be held responsible for knock-knees in our group. Only a few of our children had clinical rickets, and none had full-blown florid rickets.

Knock-knees and pronation were correlated at all ages. Correlation coefficients in seven age groups ranged from 0.16 to 0.55. Knock-knees tend to throw more weight on the medial border of the foot and so produce or aggravate pronation. There are other factors which may be expected to affect pronation. The older child and the adult break the full impact of the body weight in walking by "rolling" the foot (heel—metatarsal heads—toes). The small child takes off and comes down with the whole foot, or, if the foot is in valgus position, with the medial border. Considering all this and the relative muscular weakness of the small child, it is surprising that pronation is not more common. It is also interesting that our pronation ratings were not significantly correlated with age or the weight: length ratio.

Hyperextension of knees, excessive lumbar lordosis, and slumped back can be explained by the combined effects of gravity and inadequate muscle tone though other factors must also be involved. This is well illustrated by the findings in pseudohypertrophic muscular dystrophy, a disease of children which leads to extreme muscular weakness. In this condition excessive lumbar lordosis is striking and universal, a slump of the upper thoracic and cervical region is common, but hyperextended knees are not found as frequently as might be expected.

However, it appears to us that inadequate use of muscles for whatever reason (and consequent strain on ligaments) is involved in most peculiarities of children's posture and that the common defects are only exaggerations of these conditions. This applies also to characteristics which we did not rate, as prominent abdomen, drooping shoulders, etc. Limitations of joint movements and muscular rigidity which are prominent factors in the postural defects of adults are very uncommon in children over 3 years.* For these reasons the common defects are

*The newborn infant is hypertonic, showing a marked preponderance of flexor over extensor tone and frequently some limitation of passive joint movements (knees and elbows). This condition gradually disappears. Slight knee and hip flexion is still fairly common at 2 years but is quite unusual at 3.

rarely permanent.[3, 5] They tend to disappear with improvement of balance (mainly preschool period), strengthening of the musculature (a gradual process, much accelerated during adolescence), and the appearance of adult proportions (relatively smaller head, lower center of gravity). They require no treatment unless they are severe, though corrective exercises will accelerate improvement. On the other hand, defects due to other causes, whether congenital or acquired (poliomyelitis, trauma, etc.), are usually permanent and progressive if left alone.

POSTURE AS A WHOLE

We have intercorrelated ratings on the five posture variables at different ages. All the correlations were low, though some coefficients seemed significant. This brings us back to the question whether posture (aside from the last-mentioned severe and permanent defects) may be considered as a unit. We suspect that inadequate muscle action is involved in the majority of postural variations and defects of children. But the low correlations suggest that this factor (or other still obscure factors) is regional rather than general. Factor analysis of a larger group of posture variables may clarify the problem, but it is not likely that a large general factor will be found. At present regional appraisal seems preferable to rating posture as a whole.

SUMMARY

1. Rating scales for five variables of children's posture have been constructed. The scale points are illustrated by photographs. This method is more objective and more nearly quantitative than other rating methods now in use; it requires very little experience. These scales were used on approximately 1,400 photographs of children between the ages of 2 and 12 years.

2. Figures on the reliability of ratings are presented, and the merits and limitations of the individual scales are discussed.

3. The mean posture of apparently normal children deviates substantially from what is commonly considered desirable posture. At least four of the five variables showed significant age trends.

4. Some factors causing the peculiarities of children's posture are suggested. The same factors are probably responsible for the common postural defects of children. The problem of normal posture is discussed in the light of these findings.

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SIMPLIFYING THE CLINICAL DIFFERENTIAL DIAGNOSIS OF THE MOST COMMON TYPES OF CONGENITAL HEART DEFECTS

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ABBOTT,[1] by her splendid research work and her compilation of all available literature, has served to remove the mysteriousness surrounding congenital heart disease. She has standardized and grouped the many types so that the cardiologist is able to venture an opinion. However, to the average practitioner the entire problem is still one of obscurity. Our purpose in this article is to simplify the situation further so that the physician will not only be in a position to offer a prognosis, but also will be able to diagnose correctly the underlying disturbances. It is interesting to know that congenital defects of the heart instead of being rare are relatively common. Of a total of almost 4,000 individuals with heart disease in its many forms, both adults and children, registered in sixty-three cardiac clinics of New York in 1941, 6 per cent are classified as congenital. In the children's cardiac clinics the percentages of congenital cases vary from 10 to 35 per cent, the average being 21 per cent. This means that one-fifth of all children with heart disease have a congenital defect. McGinn and White,[2] in a series of 7,500 consecutive autopsies, discovered a congenital heart defect in almost 1 per cent of the cases. Surely, the congenital cardiac defect is a common but apparently infrequently diagnosed condition.

Some knowledge of the salient facts of embryology and morphology is of value in appreciating the many possible deformities. In its earliest stages the human heart closely resembles that of the primitive fishes. It is a simple tubelike structure, consisting successively, posteroanteriorly, of a sinus venosus, a common auricle, a common ventricle, and a bulbus arteriosus (Fig. 1). The tube rotates upon its long axis and soon assumes an S shape. The auricle and sinus venosus then rise posteriorly to the ventricle and tend to envelop the bulbus. The auricle, meanwhile, expands laterally. The sinus venosus opens into and is soon absorbed by the right auricle to become the superior and inferior vena cava. At about the fourth week the auricular septum begins to appear on the upper posterior part of the auricle as the septum primum. This grows downward towards the atrial canal. During the fifth week the upper posterior part of the septum primum disappears, leaving an opening, the foramen ovale. In the meantime a second septum appears alongside the original septum primum called the septum

Summary of exhibit as presented in the scientific hall of the American Medical Association Convention at Atlantic City, June, 1942.

secundum. This overlaps the first septum, and the slitlike passage of the foramen ovale intervenes between them. About the fifth week a ridge, the septum inferius, appears on the floor of the common ventricle. This is the beginning of the interventricular septum, which, as it grows, soon fuses with the endocardial cushion in the atrium and by uniting with the septum, which forms in the aortic bulb, completes the septi of the heart.

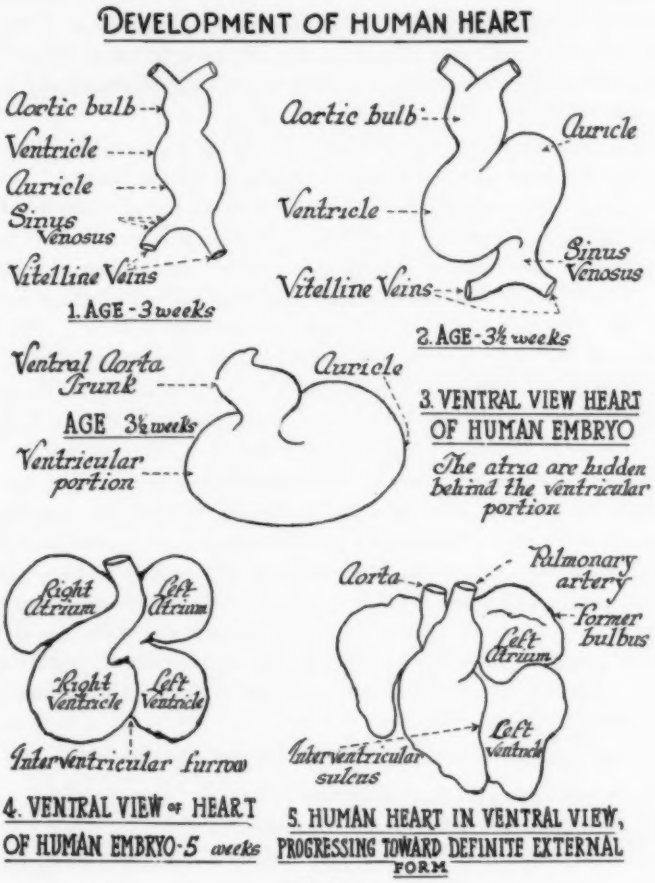

Fig. 1.

By far the most complicated and the most important metamorphosis is the rotation and absorption of the bulbus cordis. Within the bulb are several ridges which are destined to form the septa, dividing the bulbus into the aortic and pulmonary vessels. During a rotary course of approximately 180° the bulb becomes incorporated into the right ventricle to form the conus. Abnormalities in the development of the bulb lead

not only to different types of pulmonary stenosis but also to transposition of the great vessels. In general it is agreed that defective or arrested development is responsible for the greatest number of congenital heart cases. Interestingly the heart is completely developed and has all the characteristics of the adult organ by the end of the eighth week of fetal life. Therefore, all defects, with the exception perhaps of the patent ductus arteriosus, are established and set at this very early age of fetal life—an age when the entire heart is only about 3 mm. in length. It is our suspicion that even the ductus arteriosus, when it remains patent, is foredoomed at this same stage of development and is not a neonatal problem.

Our purpose, as already mentioned, is to present a simplified plan for diagnosing the most common types of congenital cardiac defects. During the period of early infancy the various congenital lesions have indefinite manifestations and very often present no signs whatsoever. This makes a diagnosis at this time not only uncertain, but most often also impossible. After this initial period the circulation and the infant become stabilized. The rare and more serious of the cardiac defects will have precipitated an early demise; the more common become manifest. We would like to say here that the much maligned patent foramen ovale, which is present in 29 per cent of all congenital cardiac conditions at autopsy, rarely, if ever, presents any signs or symptoms during life.

In the differential diagnosis of congenital heart lesions there are two important considerations: (1) the murmur and (2) the presence or absence of cyanosis. Abbott has divided congenital lesions into three groups: (a) the acyanotic, those without cyanosis; (b) the cyanose-tardive, those which may develop cyanosis; and (c) the cyanotic, those with persistent cyanosis. Again for simplification we prefer the division into two groups: those with cyanosis and those without, appreciating the fact that the latter under severe stress or strain may temporarily show signs of cyanosis.

The most common of the *acyanotic* group are as follows:

A. Patent interventricular septum
B. Patent ductus arteriosus
C. Patent foramen ovale (Rarely presents any signs or symptoms unless very large)
D. Aortic coaretation (Rarely seen except in later life)
E. Subaortic stenosis (Uncommon)

The last three may be overlooked in considering the diagnosis of common congenital cardiac defects. Therefore, the only two acyanotic congenital defects usually to be considered are the patent interventricular septum and patent ductus arteriosus.

The most common of the *cyanotic* group are as follows:

A. Pulmonary stenosis
B. Large septal lesion or triloculate heart
C. Transposition of great vessels (Usually causes death in infancy; therefore, only pulmonary stenosis and triloculate heart need be considered in the diagnosis of common *cyanotic* congenital cardiac defects)

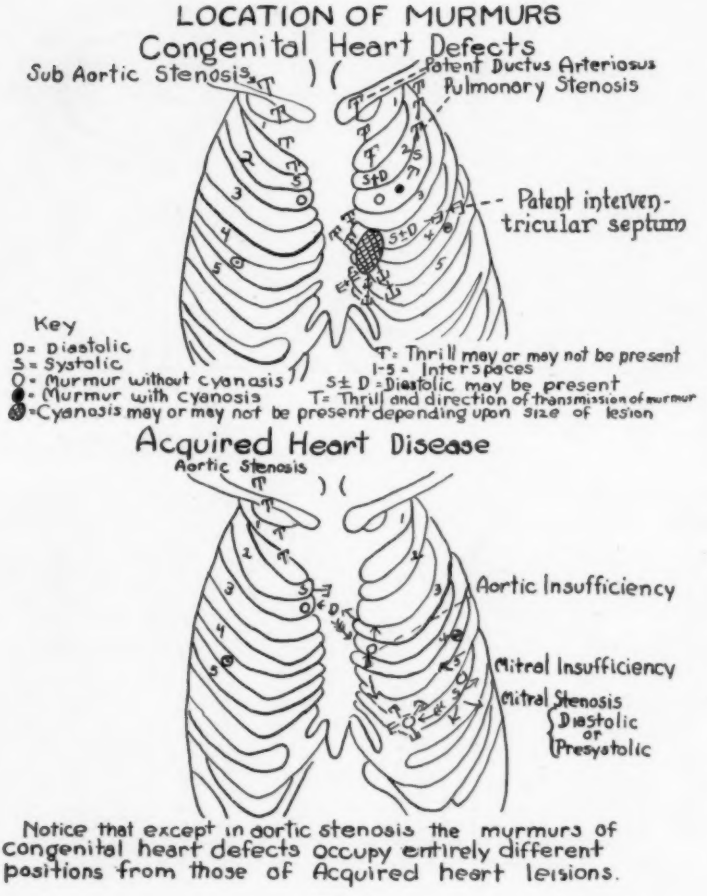
LOCATION OF MURMURS
Congenital Heart Defects
Sub Aortic Stenosis
Patent Ductus Arteriosus
Pulmonary Stenosis
Patent interventricular septum
Key
D= Diastolic
S= Systolic
O= Murmur without cyanosis
= Murmur with cyanosis
= Cyanosis may or may not be present depending upon size of lesion
T= Thrill may or may not be present
1-5 = Interspaces
S± D = Diastolic may be present
T= Thrill and direction of transmission of murmur
Acquired Heart Disease
Aortic Stenosis
Aortic Insufficiency
Mitral Insufficiency
Mitral Stenosis
Diastolic
or
Presystolic
Notice that except in aortic stenosis the murmurs of congenital heart defects occupy entirely different positions from those of Acquired heart lesions.

Fig. 2.

Two-thirds of the ninety different lesions in the one thousand cases analyzed by Abbott were either patent interventricular septum, patent ductus arteriosus, or pulmonic stenosis in primary or combined forms. Eighty per cent of the cases in the average children's cardiac clinic fall in these same categories. We feel justified, therefore, from both a

clinical and pathologic viewpoint in simmering down the complex but comprehensive analysis of congenital heart defects to the simple and most common two types in the cyanotic group and the two types in the acyanotic group. Having grouped the cases, we proceed to the analysis of the murmurs. Most important is the point of maximum intensity of these murmurs. See Fig. 2 for comparison of the location of the mur-

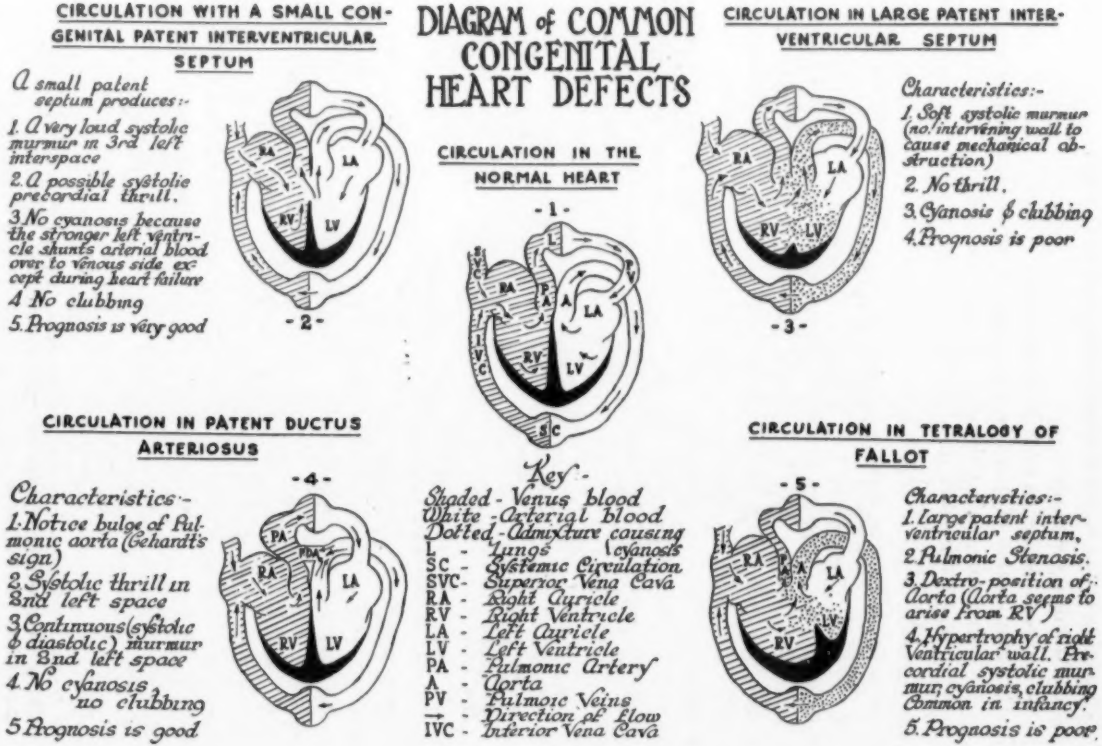

Fig. 3.

murs in the congenital and acquired heart lesions. One will instantly note the predilection of the systolic murmurs in acquired heart lesions to the apical area and of the congenital murmurs to the base and sternum. There should be no conflict between the two, provided that the point of maximum intensity is carefully ascertained.

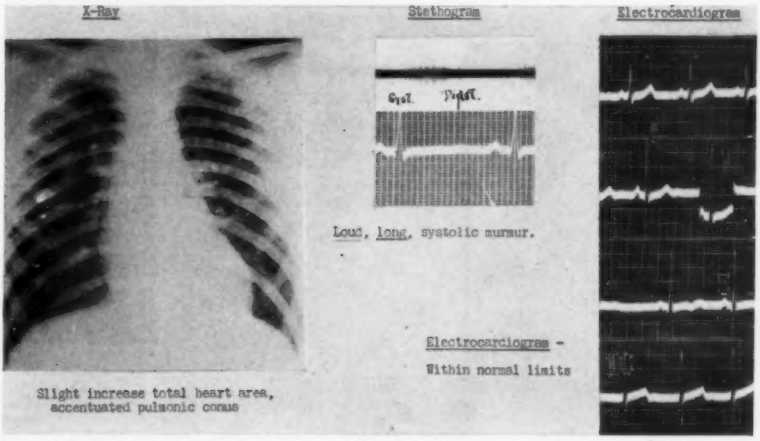

Fig. 4.—C. Z., 10 years of age. Clinical diagnosis: small patent interventricular septum.

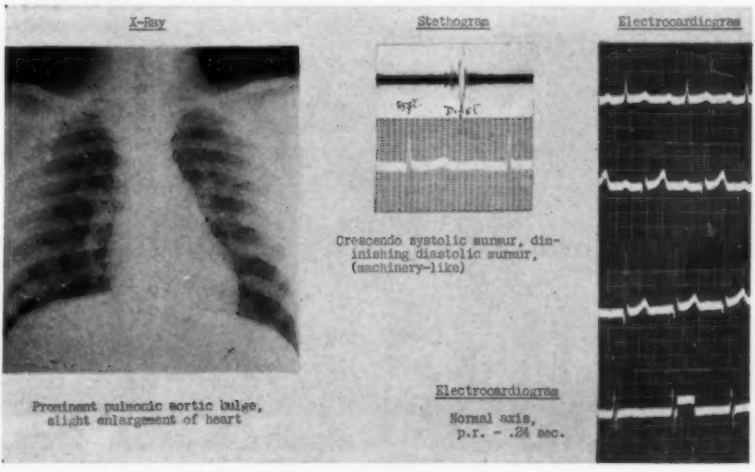

Fig. 5.—J. R., 9 years of age. Clinical diagnosis: patent ductus arteriosus.

To appreciate better the signs and symptoms of the common types of congenital cardiac lesions, five drawings are presented illustrating the physiologic basis of each. These diagrams are self explanatory and require no elucidation (Fig. 3).

How can the laboratory assist us in the diagnosis of the congenital cardiac defect? The stethogram or cardiogram is the most recent addition to our armamentarium of aids. With these we are able to time the murmurs properly and in the case of the patent ductus arteriosus, the characteristic continuous machinery-like crescendo and decrescendo

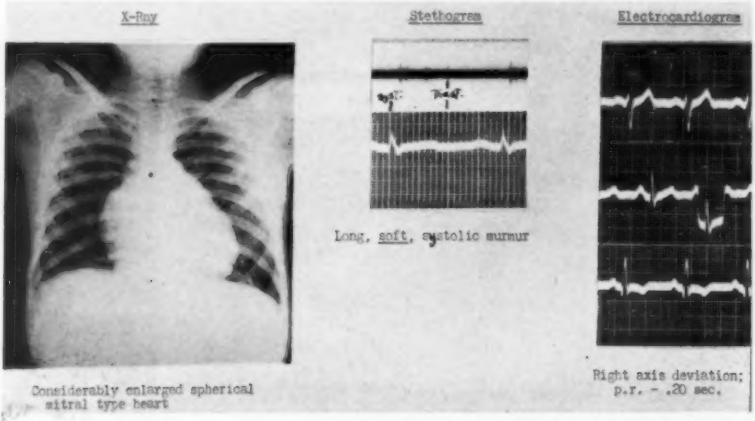

Fig. 6.—H. F., 9 years of age. Clinical diagnosis: large patent interventricular septum (associated with cyanosis and clubbing).

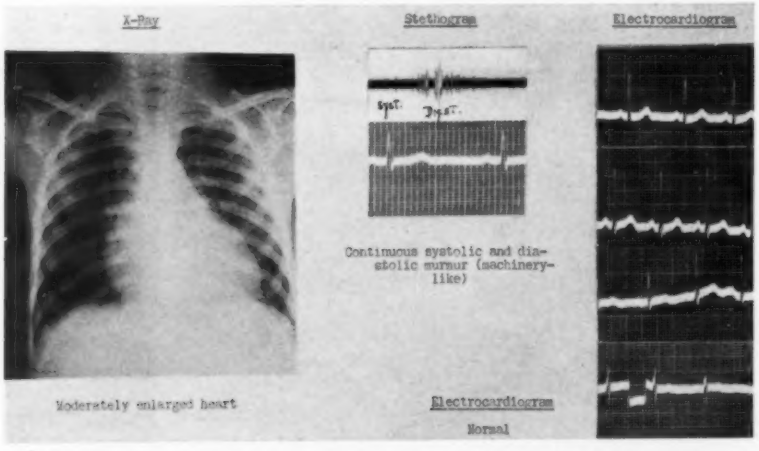

Fig. 7.—S. W., 5 years of age. Clinical diagnosis: patent ductus arteriosus.

systolic and diastolic murmurs are visualized. The murmurs of the other defects, however, except for proper timing, are not characteristic of congenital lesions.

The electrocardiogram surely should identify cardiac lesions. According to the literature and textbooks the electrocardiograph presents characteristic high voltages, or diphasic waves or deep Q waves, or right

TABLE I

DIFFERENTIAL DIAGNOSIS OF CONGENITAL HEART DEFECTS

	CYANOSIS	CLUBBING	THRILL	MURMUR	TRANSMISSION	P_2	HYPERTROPHY	PROGNOSIS
A. Patent interventricular septum	±		±S 3-4L	S+D 3-4L	Precordium	>	R+L	Good
B. Pulmonary stenosis	+++	+++	S 2L	S 2L	Base	<	R	Poor
C. Patent ductus arteriosus			±S 2L	S+D 2L	Neck	>	R	Good
Combined lesions D. A + B	+++	+++	S 2-4L	S+D 2-4L	Precordium and base	<	R+L	Poor
E. A + C			±S-L	S+D 2-4	Neck and precordium	>	R+L	Good
F. B + C	+++	+++	S 2L	S+D 2L	Neck and base	<	R	Poor
G. Trilocular heart	+++	+++		S 3-4L	Precordium	>	R+L	Poor
H. Aortic coarctation			S Sternum	±S	Back	>	L	Good
I. Subaortic stenosis			S 2R	S 2R	Neck	>	L	Good
J. Transposition of vessels	+++	+++					R+L	Poor
K. Patent foramen ovale				±S 2L		>		Good

S = Systolic.
D = Diastolic.
> = Increased.
R = Right.
L = Left.
± = May or may not be present.
Figures = Intercostal space.
< = Diminished.

axis deviation or even left axis deviation. We, however, differ and insist that there is no typical congenital electrocardiogram. In the majority of patients the electrocardiograms are normal. Occasionally a left axis deviation is obtained which is not particularly abnormal. When right axis deviation is present, it merely indicates a right heart preponderance, a condition seen in anyone with rheumatic mitral disease with a hypertrophied right ventricle. A right axis deviation is rarely present in a patent ductus arteriosus; its presence in a suspected clinical case always intimates either a complicating defect or an incorrect diagnosis. So here again the laboratory cannot make the diagnosis but may be of assistance in corroborating a clinical opinion.

The roentgenogram—that is the answer. Let the x-ray specialist make the diagnosis. But here again we are doomed to disappointment. The patent ductus arteriosus pictures a relatively normal-sized heart with a convex pulmonic aorta (Zinn's cap). This type of roentgenogram in an individual with characteristic clinical signs of patent ductus arteriosus will be of aid in clinching the diagnosis, but in the other common types of congenital cardiac defects the roentgenogram will either be that of a normal heart or an enlarged mitral-type heart. The so-called typical *coeur en sabot* or boot-shaped heart is frequently described but rarely seen. So one can readily understand that the laboratory may assist but cannot diagnose the congenital cardiac. Clinical data must still be the chief basis for diagnosis.

SUMMARY

Realizing the relative frequency of congenital cardiac defects and the difficulty in differentiating the ninety types, the many rare and unusual kinds are eliminated in a plan for the simplification of the clinical differential diagnosis of the most common varieties. We discuss the cardinal features in the embryology of the human heart together with the characteristic clinical findings in the two most common cyanotic types (pulmonary stenosis and large septal lesion) and the two most frequent acyanotic types (patent ductus arteriosis and small patent interventricular septal lesion). Figures showing the pathologic changes and physiology of the different lesions are presented. The diagnostic importance of stethograms, electrocardiograms, and roentgenograms is analyzed.

The authors wish to acknowledge the kind assistance of Rev. Paul Hoover.

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PORENCEPHALY

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PORENCEPHALY often results in a syndrome which merits clinical recognition. Of the five cases presented in this small series, we were able to make a correct clinical diagnosis in three of the patients. The necessity for clinical diagnosis cannot be overemphasized, for it leads to both confirmatory diagnostic procedures and treatment, the latter perhaps alleviating the condition entirely or in part. Hospital ward cases run in cycles, yet it is a peculiar accent on the cycle when four of the five cases reported occurred in the last year and only one other in the past fourteen years. It leads to the supposition that either this is one of the whimsies of chance or that our diagnostic acumen has improved in the last year.

Definition.—It may be said that all our patients with porencephaly had a cerebral cortical cyst extending from the surface of a hemisphere to or into the lateral ventricle. The modern understanding of a porencephalic cyst has been aptly stated by LeCount and Semerak[1] as follows: "A defect communicating with the ventricles or separated from them by a thin layer of brain tissue and covered on the outside by the arachnoid." Many limitations and extensions of the meaning of porencephaly have been attempted since the original definition by Heschl[2] on the basis of eight cases reported from 1859 to 1868. He limited porencephaly to "the presence of cysts or cavities in the brain cortex, communicating with the arachnoid space and penetrating deeply into the brain due to an arrested development or to congenital disease that produces atrophy of the brain." He later admitted the possibility of a traumatic origin. Bourneville and Schwartz[3] attempted to differentiate between true and false porencephaly on the basis of a vascular or nonvascular etiology. Siegmund[4] classified only lesions due to destruction without infection as porencephaly. He does not ascribe to the congenital origin of this condition. Oberstiener[5] defined a pseudoporencephaly as a porus not in communication with the ventricle, and Kundrat[6] applied the same name to a cyst roofed by arachnoid.

Etiology.—As always, when the etiology of a pathologic entity is obscure, numerous theories appear in the literature. Again, when a clear-cut definition of porencephaly, as stated by LeCount and Semerak,[1] has just recently emerged from the voluminous mass of literature on the subject, it is hardly to be expected that any conclusive investigative

From the Pediatric Department, New York Postgraduate Medical School and Hospital.

work would have been completed. Kaufman[7] originally divided porencephaly into the typical and secondary types. Typical types were purely congenital and of dysontogenic origin, while secondary types were due to trauma, vascular defects, or infection. Kaufman later pointed out that Beyer[8] has shown beyond the shadow of doubt that there is really no fundamental difference in the development of congenital or acquired porencephaly and that the same causes which have been demonstrated in acquired porencephaly occur in congenital cases.

Vascular disturbances as the basic cause of porencephaly was propounded by Heschl,[2] the originator of the term porencephaly. Kundrat[6] supported this theory, although claiming that the cysts are infrequently acquired, the congenital ones usually originating on the basis of vascular defects. LeCount and Semerak's[1] third case was probably of vascular origin. Patten and Alpers[9] and Holtby[10] support this theory. At least if not responsible for all, vascular defects, such as hemorrhage, embolism, venous disturbances, and abnormal blood supply are responsible for a limited number of porencephalies.

Inflammatory lesions, such as encephalitis, syphilis, tuberculosis, and other infections, are certainly the underlying cause in many instances. Winterode and Lewis[11] presented a case of porencephaly with definite evidence of tuberculosis. LeCount and Semerak's[1] fourth case had a meningo-encephalitis of syphilitic origin. A case of porencephaly due to encephalitis is analyzed in detail by Globus.[12] Others supporting this theory are Benedek and Thurzo,[13] Levaditi, Lepine, and Schoen,[14] Wigglesworth,[15] and Virchow.[16] Jaffe[17] questions the whole theory of infectious origin in that "the presence of inflammatory changes in a brain with a porencephalic defect does not necessarily mean that the inflammation has produced the defect."

Trauma as a cause of porencephaly may occur at any point in life—while in utero (Kikuth[18]), during birth, or in later life. Schwartz[19] has been especially instrumental in pointing out the possible mechanism of development of porencephalic defects following birth trauma. Jaffe[17] reported a cyst resulting from trauma immediately after birth and an excellent summary of the case for trauma. Kastein[20] and Schroer[21] are others who support this theory. Certainly trauma must be accepted as one of the major causes of porencephaly.

There is the greatest possibility that porencephaly is an end result of multiple causes, and one etiologic factor cannot be selected as a constant underlying fault. Our cases have little to add to the multiplicity of causes. Three patients had a history of difficult labor, two had forceps applied to facilitate labor, and one of these was cyanotic at birth. The third patient had a twenty-four-hour difficult prolonged labor. Another one had an indefinite history of poliomyelitis at 3 months of age, and the onset of convulsions and paralysis was immediately preceded by fever and vomiting. The age of onset of noticeable signs and symptoms might perhaps give some indications to the etiology. Three of our

patients showed an onset in the first year of life. Two of these had a history of difficult labor. The other two patients first presented symptoms in early childhood. Schattenberg[22] reported twelve deaths, of forty-six cases autopsied, occurring during the first year of life, at least suggesting the possibility of an early onset of porencephaly.

To draw any conclusions as to traumatic, infectious, or vascular origin of porencephaly on the basis of this series is impossible. It is interesting to note that in a case of brain cyst, omitted from this series because of its gliomatous origin (Kennard[23] presents a porencephalic cyst on this basis), a typical porencephalic cyst was found at operation.

CLINICAL HISTORY, SIGNS, AND SYMPTOMS

Symptom Complex.—Clinical recognition of porencephaly is a definite possibility in many cases. In four of our five patients the diagnosis was definitely suspected before roentgenographic confirmation. In Patten, Grant, and Yaskin's[24] excellent clinical review of nine cases, eight presented a clinical picture which would lead one to consider a diagnosis of porencephaly. The "complete" syndrome necessary for a diagnosis consists of two findings, hemiplegia and Jacksonian convulsions, both involving the same side of the body. These two factors alone are enough to make a clinical diagnosis of porencephaly tenable.

Frequently mental deficiency also occurs. Less frequently hemianopsia, complete blindness, facial paralysis, and sensory disturbances are present. All these accessory findings complicate the picture and make a clinical diagnosis more difficult.

One should always investigate the possibility of a difficult labor, infection in the mother before labor, infection in the patient preceding the onset of the syndrome, traumatic cranial injury, and a delayed developmental course. Any degree of actual clinical involvement may be present from our so-called "complete" clinical syndrome, plus other mentioned findings, to an absolutely "silent" porencephaly. The clinical expression of a porencephaly naturally depends on its location, size, and time of onset. A "silent" porencephaly, or one that gives no signs or symptoms, is best exemplified by the patient in our first case who had bilateral porencephalic defects, but the defect in the left parietal area failed to manifest itself clinically.

In addition, on the basis of a history of prolonged labor, one might surmise that the porencephaly was present in the patient in our fourth case from some time immediately after birth yet was silent up until the age of 10 years. Even at that time she showed an incomplete syndrome having only nocturnal convulsions.

Birth History.—In contrast to Patten, Grant, and Yaskin's[24] series in which only one of nine patients gave a history of birth difficulties, three of our five cases had this background. Two of these three cases showed an early onset of their syndrome.

Developmental Retardation.—Four of our patients showed some developmental retardation. Only one, the patient in our last case, showed

any marked retardation and even that was not very severe. It is of interest that the fourth case which was "silent" until the patient reached the age of 10 years showed no developmental retardation.

Mental Retardation.—Of the five patients only one (Case 5) showed any marked mental retardation. The patient in Case 2, although not mentally retarded, did show some psychic peculiarities. Bianchi[25] found that of sixty-one reported cases which he analyzed, at a minimum twenty-one of the patients were abnormal, although there may have been more.

Convulsions.—Four of our five patients had convulsions. Of these, three were typical of the "complete" syndrome; that is, Jacksonian in type and limited to the side showing motor paralysis. The convulsions and motor paralysis, of course, occurred on the side opposite to the porencephaly. The length of these convulsions varied from two to ten minutes in the average case, and up to two hours in the fifth patient. In most instances the onset of motor paralysis and convulsions occurred simultaneously. The exception was the patient in Case 1, which, although showing a "complete" syndrome, had the onset of motor paralysis at 6 months of age while the convulsions did not begin until 6 years of age. In our fourth patient the only manifestation of porencephaly was the convulsions, and these were generalized in character. Both the fourth and fifth patients had nocturnal convulsions only.

The second case is especially interesting from the convulsive angle. Although the patient definitely had no convulsions, the electroencephalogram showed occasional spike and dome waves over the porencephalic area, these waves being characteristic of epilepsy. McLean[26] was of the opinion that she definitely had the tendency to convulsive phenomena and would have eventually had convulsions. He predicated the theory that operation would break the electrocortical activities responsible for these waves and that the convulsive tendency would then disappear. He was also of the opinion that in many instances these convulsions were due to meningeal cortical adhesions, and, on operating, always released these adhesions. It is unfortunate that we were unable to have an electroencephalogram following the operation on the patient in the case just described, for had the spike and dome waves disappeared, it would have partially sustained McLean's theory of the origin of these convulsions.

Motor Paralysis.—Paralysis and weakness of the involved side was present in four patients. It took the form of spastic hemiplegia in all four. There was marked atrophy of the hemiplegic side and contracture deformities. These contracture deformities consisted mainly of claw hand, partial flexion of elbow and knee, and, in two instances, an equinovarus. There was definite weakness of both the involved arms and legs in all four patients. Three of the patients (Cases 1, 3, and 5) showed shortening of one or the other of their extremities in addition to their atrophy. Three (Cases 1, 2, and 3) had a facial paralysis on the same side as their hemiplegia. There was only one other motor

finding in the series and that was a lateral deviation of the left eye (Case 2). Three of the patients (Cases 1, 2, and 3) had an onset of motor paralysis under 1 year of age; the other (Case 5) began at the age of 3 years.

Other Findings.—Other findings such as hemianopsia, sensory findings, and aphasia have been reported but were not present in this series.

CONFIRMATORY DIAGNOSTIC PROCEDURES

Since there are other pathologico-neurologic conditions that might occasionally account for clinical findings resembling even the "complete" porencephalic syndrome, confirmation of the diagnosis of porencephaly is necessary before any surgical procedures can be contemplated. Of these procedures, encephalogram is the most important, ventriculogram sometimes necessary because of the occasional mechanical errors that may arise in an encephalographic procedure and electroencephalogram helpful in that it may give some indication of approximate location of the defect.

Encephalogram.—In all but two patients (Cases 1 and 5) porencephaly was demonstrated by encephalographic studies. In the two cases some mechanical obstruction may have interfered with the rise of air into the cystic defects. Both these patients were later shown to have porencephalic cysts, one by ventriculogram, the other by surgery. The only criteria necessary for the encephalographic diagnosis of porencephalic cyst is as follows:

1. Cyst or cysts of the brain, in most instances in communication with the lateral ventricles. In addition, there are other confirmatory diagnostic criteria which may or may not be present.
2. Evidence of atrophy of brain.
   (a) Enlargement of the subarachnoid spaces, unilateral or bilateral.
   (b) Atrophy of brain hemisphere containing defect will often cause a noticeable shift of ventricular system toward the defective hemisphere.
   (c) Ventricular distortion and dilatation dependent upon the amount of atrophy present.
3. Evidence of arachnoiditis. Arachnoid space on same side as cyst may be obliterated.

Cystic degeneration of a glioma is the chief lesion which must be differentiated from a porencephalic cyst. This differential can be made when the following are noted:

1. Ventricular shift is toward the side opposite that of the lesion.
2. There is none or only slight evidence of cerebral atrophy.
3. Ventricular system usually normal or shows encroachment rather than dilatation.

Ventriculogram.—The criteria of diagnosis are, of course, the same as those of encephalogram. The advantage of a ventriculogram is the direct injection of air into the ventricular system and the consequent removal of some of the mechanical factors which might interfere with the rise of air in an encephalogram. Case 1 is a good example of this, for a "silent" porencephaly was missed by encephalogram, but demonstrated by ventriculogram. We were fortunate in having the ventriculogram in Case 1 done with the contrast material of Lefft and McLean[27] and superior results can be seen in Fig. 2.

Electroencephalogram.—This is a newer diagnostic procedure which is usually resorted to before encephalogram. Its usefulness, as Pacella and Barrera[28] point out, "is not (as) an indicator of individual clinical entities, with a possible exception of petit mal epilepsy, but that it is related primarily to the electrophysiologic state of the cortex." It cannot be expected that the electroencephalographic procedure will give an indication as to the underlying pathology but will perhaps locate the pathology and occasionally give some other information. In the patient in Case 1 abnormal electrocortical activity was recorded posterior to the actual porencephaly. Pacella and Barrera,[28] in speaking of tumors, point out that "it is the disturbed tissue immediately surrounding the tumor which gives rise to the abnormal brain waves and not the actual tumor tissue or any surrounding dead cortical substance." The same may hold to some extent in porencephaly and account for the posterior location of abnormal electrocortical activity in this case. In the patient in Case 2 location of the cyst by electroencephalogram was in accordance with its actual location and in addition showed a tendency to convulsions which could not have been demonstrated by any other method. In Case 3 the electroencephalographic findings, although finding the difficulty in the frontal area, failed to locate the involved side. Electroencephalographic studies are of limited value in porencephaly, giving some indication of the location of the cyst and occasionally the tendency to convulsions.

LOCATION

In our five patients three of the cysts occurred in the right hemisphere, two in the left. In Patten, Grant, and Yaskin's[24] series, eight out of nine cysts were in the left cerebral hemisphere. In Siegmund's[4] series 14 per cent of the cysts occurred in the occipital lobe.

Three of our patients had defects in the frontoparietal area (Cases 2, 3, and 4), while two occurred in the temporoparietal area (Cases 1 and 5). This agrees more or less with Siegmund's report of 122 cases in which the region of the central fissure was most frequently involved.

The presence of multiple cysts is not a too frequent occurrence. Holtby[10] and LeCount and Semerak[1] have reported cases. Our first case was one of bilateral porencephaly, the one on the left being "silent."

Clinical signs are, of course, in part dependent upon the location of the cyst, but also to an equal extent on the size of the defect. The size

of some of these cysts showing a minimal amount of clinical evidence is sometimes astonishing. Spatz,[29] as a result of his work on newborn rabbits, has attempted to explain this on the basis of the greater adaptability of the newborn brain; the same size cyst originating in adult life would perhaps lead to fatality.

TREATMENT

Surgery.—The surgical problems attached to a successful alleviation of porencephaly in part or whole are multiple because of the varied gross pathology which may be present at operation. In our operative cases the surgical technique might be divided into five parts, all or only a few of the procedures necessarily being used at one operation.

1. Removal of portion of arachnoid overlying the porencephalic mass.
2. Release of any cortical dural adhesions.
3. Evacuation of contents of cyst.
4. Incision of any trabeculae which may be found in cyst.
5. Insure adequate drainage of porus into the lateral ventricles and subarachnoid space.

The purposes of the above procedures are almost self-evident, first, to release any adhesions that may perhaps account for the convulsive phenomena, and, second, to insure adequate drainage of the defect so that an area of increased pressure in the brain can be avoided in the future.

The surgical pathology found in Cases 1 and 2 was similar. Both patients presented a thin, atrophied, grayish cortex showing ghosts of previous cortical convolutions overlying the cyst. In both instances the porencephalic mass was gelatinous to the feel, with many blood vessels traversing the mass. In the second case there were trabeculae throughout, isolating areas of spinal fluid. Communication of the defect with the lateral ventricle in this case was blocked by a valvelike flap which was incised in an avascular area. The cyst in the patient in the fifth case was similar to those in the patients in the first and second cases but much larger.

The results of surgery were certainly hopeful, although they must be tempered by the shortness of the follow-up. Definite improvement in the motor paralysis was noted in all three operative cases, actually remarkable in Cases 1 and 2. Here even before discharge from the hospital noticeable improvement had occurred, and within four months it was difficult to notice any paralysis in the patient in Case 1 unless a physical examination was performed.

Convulsions recurred in the patient in Case 1 some six months after operation, but they were nowhere near as severe as previously. It is too early to determine their frequency. In the fifth case there had been a definite decrease in the number and severity of convulsions. In this case there had also been some improvement in the mental status of the child, since he has begun to progress in school.

TABLE I

CASE	SEX AND AGE	BIRTH HISTORY	DEV. RETARDATION	AGE OF ONSET	CONVULSIONS	AGE OF ONSET	MOTOR PARALYSIS	ENCEPHALOGRAPHIC OR VENTRICULOGRAPHIC LOCATION OF CYST	ELECTROENCEPHALOGRAM	TREATMENT	RESULTS
1. R. H.	M., 6 yr.	Forceps	Slight	6 yr.	Jacksonian—left sided; one monthly; ten minutes' duration	6 mo.	Left spastic hemiplegia; left facial	1. Right temporoparietal area; (2) left parietal area	Abnormal electrocortical activity—right occipital region	(1) Evacuation of cyst; (2) release of dural adhesions; (3) improved communication of cyst with ventricular system	(1) Marked improvement of motor paralysis; (2) Decrease in severity of convulsions
2. J. S.	F., 6 yr.	Precipitate delivery	Slight	9 mo.	None—electroencephalographic evidence of convulsive tendency	9 mo.	Left spastic hemiplegia; left facial; lateral deviation of left eye	Right frontoparietal area	Abnormality over right motor area with occasional spike and dome wave	(1) Evacuation of cyst; (2) dissection of porencephalic mass; (3) improved communication of cyst with ventricular system	(1) Marked improvement of motor paralysis

3. A. T.	F., 11 yr.	Forceps; cyanosis at birth	Slight	3 mo.	Jacksonian—right sided; one monthly to three to four weekly; two to ten minutes' duration	3 mo.	Right spastic hemiplegia; right facial	Left parieto-frontal area	Diffuse abnormality over frontal area	Incomplete	
4. L. G.	F., 10 yr.	Prolonged labor		10 yr.	Generalized; nocturnal; monthly intervals; two to ten minutes' duration	10 yr.	None	Right paracentral lobule		Sodium dilantin gr. 1½ twice daily	Disappearance of all convulsions
5. J. A.	M., 10 yr.	Normal	Moderate	3 yr.	Jacksonian—right sided; nocturnal; two to three weekly; two to 120 minutes' duration	3 yr.	Right spastic hemiplegia	Negative—operation revealed left temporoparietal cyst		(1) Evacuation of cyst	(1) Some improvement of both motor and convulsive disorders; (2) improvement of mental status

The patients in Cases 1 and 2 were right-handed individuals with a porencephalic defect on the right side and the motor involvement on the left. It is not presumptuous to assume, had the situation been reversed in a right-handed individual, that the surgical results as far as the motor paralysis were concerned would not have been as good, since the particularly vital centers in a right-handed individual would have been involved.

Medical Treatment.—Medical treatment was feasible in only one patient (Case 4). This child had convulsions which were completely controlled by sodium dilantin.

SUMMARY

1. Porencephaly is a cystic defect of the brain communicating with the ventricles or separated from them by a thin layer of brain tissue and covered on the outside by the arachnoid.

2. A clinical diagnosis is often possible, based upon the "complete" syndrome of Jacksonian convulsions and paralysis of the arms and legs, or both, the convulsions and paralysis being limited to the same side of the body. Limitations or extensions of this syndrome occur, ranging from the "silent" porencephaly to one manifested by the "complete" syndrome plus hemianopsia, blindness, sensory changes, mental retardation, and various other findings.

3. This clinical diagnosis can be confirmed by encephalography and ventriculography, and valuable information can be obtained from an electroencephalogram.

4. Surgical intervention will often result in marked motor improvement and relieve the convulsive phenomena partially or entirely.

CASE 1.—"Complete" syndrome with good operative results. Bilateral porencephaly, the left one being silent.

R. H., male, 6 years, 3 months of age, was admitted to the hospital on Sept. 9, 1941. The chief complaints were weakness of the left arm and leg since 6 months of age and convulsions for the past six months.

History of Present Illness.—Forceps delivery, following a twenty-four-hour difficult labor. At birth the infant had no convulsions, vomiting, or cyanosis. At 6 months of age his parents noticed failure to use the left hand. Weakness of the left leg was noticed when he began to walk. He was hesitant of speech and often repeated himself. When about 6 months of age the child had a convulsion involving the entire left side of his body which was accompanied by loss of consciousness. Three or four more convulsions of the same type occurred up to time of admission to the hospital. He also complained of frequent morning headaches, sometimes accompanied by dizzy spells. Development was slightly retarded: first tooth at 14 months; sat at 9 months; stood at 10 months; and walked and talked at 15 months.

Past History and Family History.—Noncontributory.

Physical Examination.—Negative except for neurologic findings.

Neurologic Findings.—Left arm three-fourths of an inch shorter than the right; moderate clawlike left hand; left arm almost useless because of spasticity; atrophy of the left calf muscles noticeable; left foot drop and elevation of the left heel on walking; generalized hyperreflexia of entire left side of body with associated loss of use of abdominal muscles and a positive left Babinski reflex; walked with

decided limp and dragged the left foot; unable to run because of spasticity of left leg.

Laboratory Examination.—Routine procedure, including spinal fluid and Wassermann tests; findings were negative.

Electroencephalogram (briefed).—Short runs of waves of six cycles per second were noted over all regions of the brain, and a moderate amount of from 9 to 10 cycles per second waves, all of high amplitude, were noticed over the parieto-occipital regions, more so on the left than on the right. At times suspicious dome and spike pattern forms were noted over the parieto-occipital areas, but this was not very definite. The occipital region on the right side exhibited a greater incidence of slower waves of from 2 to 4 cycles per second, exhibiting higher amplitude than does the parietal area on the left side, but the entire right parieto-occipital regions showed more slow waves than did the left.

Fig. 1 (Case 1).—Encephalogram. Irregular large collections of air in the right temporoparietal area, with poor filling of the ventricles.

Impression.—The record was suggestive of a focus of electrocortical abnormality in the right occipital region. It was difficult to state the character of the disturbance in the brain which was resulting in this abnormality. However, the absence of definite sustained dome and spike forms plus the localized area of abnormality noted were not definitely suggestive of idiopathic epilepsy.

Encephalogram.—Examination showed an irregular, large collection of air in the right temporoparietal area with poor filling of the ventricles. There was an apparent dilatation of the lateral ventricles on the right (Fig. 1).

Ventriculogram.—Injection of contrast media on the left side revealed an irregular distribution of the contrast media with apparent cortical retraction of a large, irregular cystlike area in the mid-lower left parietal area. None of the contrast medium had apparently reached the ventricular system. The area was quite irregular in contour, roughly rectangular in shape, three inches in length, and somewhat over one inch in diameter, roughly paralleling the lower parietal area. (The area just described was on the opposite side to the large air pocket with

cortical retraction previously described on the right in the encephalogram report.) Further injection of the ventricular system from the right side showed a dilatation of the ventricles, with a lateral horn on the right somewhat larger than that on the left, with moderate compression discernible on the left side and moderate shift of the whole ventricular system to the right (Fig. 2).

Operation.—The dura over the right frontotemporal area was incised in a circular fashion and reflected toward the temporal fossa, exposing a soft mass of jellylike material having the appearance of tapioca pudding and occupying the inferior superior portion of the Sylvian fissure. There was atrophy of the cortex underlying this and many blood vessels traversing the gelatinous material with ghosts of cortical convolutions remaining in the gelatinous area. The arachnoid overlying this entire mass was stripped loose clear down to the Sylvian fissure, and a portion of it

Fig. 2 (Case 1).—Ventriculogram with contrast material; left cortical retraction due to a large irregular cystlike area in the mid-lower left parietal area. Also shows right porencephaly. No contrast media in ventricles.

was removed with the electrocautery. This succeeded in draining a large amount of spinal fluid from the cyst which left a saucer-shaped defect. Exploration of the posterior margin of the bony opening revealed the cortex to be firmly attached to the dura in about four or five areas on the margin of the gelatinous tissue. These were severed from the dura. Two or three additional openings were made into the subarachnoid space, communicating the atrophic areas with the spinal fluid system. The frontal horn of the right lateral ventricle was needled through the cauterized area of the cortex with a large brain cannula, communicating the right lateral ventricle with the area.

Pathologic Report.—Glial and connective tissue scar of pia-arachnoid.

Course.—Within one week the patient showed improved motion in the left hand and talked spontaneously. He has had two convulsions occurring six months after

operation. These were less severe than his previous convulsions and lasted only a minute or two. He now walks and runs without a limp and has recovered most of the function in his left upper extremity.

Comment.—This case is noteworthy both for the remarkable results of operative intervention and the existence of a second silent porencephalic cyst on the left side. We have maintained the existence of silent porencephalic defects previously, but the occurrence of a silent porencephaly and one resulting in a complete syndrome is a rarity. That the left porencephalic cyst did not appear in the encephalographic studies can only emphasize the occasional necessity of doing a ventriculogram. This is the case previously mentioned in which the contrast material of Lefft and McLean was used for ventriculographic studies. Figs. 1 and 2 show its superior results. Operative results were good. This boy was shown at a meeting of the New York Academy of Pediatrics where he took special delight in running about the room for the benefit of the audience. He was unable to run previous to operation.

CASE 2.—Incomplete syndrome with hemiplegia was the only clinical manifestation, although there was electroencephalographic evidence of convulsive tendencies.

J. S., female, 5 years, 8 months of age, was admitted Sept. 30, 1941. The chief complaints were weakness and spasticity of the left side of the body since 9 months of age.

History of Present Illness.—Full term; precipitate spontaneous delivery, labor lasting twenty minutes. The sucking reflex was poor at birth, and feeding was difficult; frequent projectile vomiting up to 2 years of age. Weakness of the left side noted at 9 months; weakness became prominent when child began to walk at 2½ years of age; walked with a limp and dragged the left leg; left hand generally held in flexed position; no convulsions, loss of consciousness, headache, dizziness or fainting; Development retarded: first tooth at 1 year, sat at 1 year, stood at 2 years, walked at 2½ years.

Past History and Family History.—Noncontributory.

Physical Examination.—Negative except for neurologic findings.

Neurologic Examination.—Lateral deviation of left eye; left pupil reacted sluggishly to light; generalized atrophy, spasticity and weakness of the left arm and leg; no Babinski reflex; left hand clawlike and left foot apparently ankylosed in hyperextension; dragged the left leg in walking.

Laboratory Examination.—Routine procedure, including spinal fluid and Wassermann tests; findings were negative.

Electroencephalogram.—The record showed a fairly marked irregularity in the pattern of the entire cortex, with frequent appearance of waves of high amplitude of from 1.5 to 3 cycles per second. Slow waves appeared to be most pronounced over the right motor and the left occipital regions. At times the slow potentials appeared serially for a short period of time, and infrequently a spike and dome pattern was noted, appearing synchronously bilaterally.

Impression.—The record suggested that there was some degree of generalized electrocortical abnormality with an area of increased abnormality in the right motor region and possibly also in the left occipital region. The pattern was not suggestive of any neoplastic condition.

Encephalogram.—Considerable right ventricular distention with a large cystlike area fully 3 to 5 cm. in diameter in the right frontal parietal area, this apparently communicating with the anterior third of the lateral ventricle and resulting in considerable cortical atrophy (Fig. 3).

Operation.—The dura over the right frontotemporal area was opened, exposing a grayish white gelatinous-like mass, occupying approximately the position of the motor area. There was no significant attachment of this mass to the dura. However, there were trabeculae throughout, isolating areas of spinal fluid. The vascular markings within the gelatinous mass had the distribution and appearance of previous cortical convolutions. The entire mass was dissected from the Sylvian fissure upward, and opposite the posterior end of the second frontal convolution there was a direct communication with a portion of this mass and the right lateral ventricle. The communication with the lateral ventricle was in the nature of a valvelike flap

Fig. 3 (Case 2).—Encephalogram. Considerable right ventricular distention with a large cystlike area in the right frontoparietal area.

which was incised in an avascular area and turned back to allow free communication of the lateral ventricle and the subarachnoid space laid bare by dissection of the porencephalic mass.

Pathologic Report.—Glial and connective tissue scar of pia arachnoid.

Course.—Left strabismus disappeared after operation, and there was much less spasticity on the left side. Two weeks after operation no spasticity could be detected and reflexes were almost normal. After three weeks, the patient was beginning to walk and, though she still limped, was flexing her left knee and not dragging her left foot as she had done previously when walking. The child returned to South America, and further follow-up could not be made.

Comment.—It has been suggested that the convulsive tendencies in this patient might have been due to tension placed upon the trabeculae rather than to dural cortical adhesions as in the patient in Case 1.

CASE 3.—"Complete" syndrome with surgical intervention postponed because of excessive bleeding during craniotomy (Fig. 4). A. T., female, 11 years of age, was admitted to the hospital Dec. 1, 1941. The chief complaints were convulsions and weakness of left side since 3 months of age.

History of Present Illness.—Instrumental delivery following a difficult fifteen-hour labor. Cyanosis occurred immediately after birth but did not recur. From 3 months to 4 years of age she had frequent right-sided convulsions and as she grew older had persistent right-sided weakness and spasticity. From four to eleven years of age she had no convulsions but did have occasional episodes resembling

Fig. 4 (Case 3).—Note typical atrophy of right side of body, especially the arm.

petit mal. In the past one and a half years she had had four right-sided convulsions, three of them over a period of five days three weeks before admission; development was within slow normal range. Family history was noncontributory.

Physical Examination.—Normal except for neurologic findings.

Neurologic Findings.—Lower right facial weakness; spasticity, weakness and lack of coordination of right upper and lower extremities; athetoid movements and moderate clawing of the right hand; atrophy of muscles of right hand and leg. The child walked with a decided right limp; hyperreflexia on right (Fig. 4).

Laboratory Examination.—Complete blood count and urine, normal; Wassermann, negative; basal metabolic rate, 19 per cent below normal. Spinal fluid normal except for 100 lymphocytes per cubic millimeter.

Electroencephalogram.—There appeared to be a slightly greater incidence of slow waves than is seen in the records of the average 11-year-old child. Therefore, some degree of diffuse abnormal electrocortical activity, particularly over the frontal regions bilaterally, apparently was present. The character of the pattern was not suggestive of any localized lesion but could be more consistent with a clinical diagnosis of epilepsy. However, the record was not particularly characteristic for this disorder in view of the absence of spike and dome patterns.

Encephalogram.—Deviation of ventricles toward the left with collection of air in the subarachnoid space mainly in the left parietofrontal region.

Operation.—Porencephalic cyst was identified at operation but due to profuse hemorrhage, which was sustained during this procedure, it was thought advisable to do a second stage sometime later.

Course.—Because of a persistent draining sinus at the posterior border of the wound, the patient was sent home to return at a future date for a second-stage operation.

CASE 4.—Porencephaly in which the only manifestation was nocturnal convulsions. These were controlled with sodium dilantan. L. G., female, 10 years, 6 months of age, was admitted to the hospital Nov. 28, 1940. The chief complaint was nocturnal convulsions at about monthly intervals for the last four months.

Present Illness.—Four months previously the child's father noticed generalized convulsive movements, including rolling of eyes, clamped jaws, and streaked, foamy saliva. The attack lasted ten minutes after which the child awakened with no knowledge of what had happened. Twice since this original attack the father found blood-stained saliva on the pillow. The day before admission the child had a convulsion similar to the one described above. Full-term normal delivery but a twenty-four-hour prolonged labor; the child apparently was normal at birth. Development was normal. Past and family history was noncontributory.

Physical Examination.—Negative.

Encephalogram.—The flat plate of skull showed increased convolutional markings more marked in the frontal and right parietal region. The air studies showed a cyst cavity (2 cm. in length) communicating with the subarachnoid space (probably also with ventricle) on the right side in the paracentral lobule just behind the motor area at the vertex.

Laboratory Examination.—Negative.

Treatment.—Sodium dilantin, 1½ gr., twice daily. The neurosurgeon first suggested craniotomy with the usual operative procedures. He suggested that the longer the patient has seizures the more likelihood there was of establishing an irreversible convulsive pattern. At the instigation of the pediatrician, she was started on a course of sodium dilantin, gr. lss twice daily, with the stipulation that if convulsions continued she was to have a craniotomy.

Course.—The child has been on sodium dilantin for one year without any recurrence of convulsive seizures.

Comment.—A question might arise here as to whether this child had a "silent" porencephaly with an onset of epilepsy at 10 years of age, the two conditions being unrelated. This problem is hardly resolved by the adequate results of sodium dilantin but may be answered at some future date if the patient comes to operation.

CASE 5.—"Complete" syndrome accompanied by mental retardation. Operative results fair. J. A., male, 10 years of age, was admitted to the hospital June 26, 1936. The chief complaints were paralysis of the right upper extremity and right-sided convulsions since 3 years of age.

History of Present Illness.—Birth history was normal. At 3 years of age the patient had an attack of fever and vomiting. This was followed by a spastic paralysis and atrophy of the right arm and leg. Shortly after this the child began

to have nocturnal right-sided convulsions two or three times weekly, diminishing gradually in frequency and severity up to the time of admission to the hospital. Mental retardation was noted when the patient entered school. There was a definite delay in his ability to talk and walk. Past history and family history were noncontributory except for a possible poliomyelitis at 3 months of age.

Physical Examination.—Except for noticeable poor nutritional state and mental retardation, the physical examination other than the neurologic was negative.

Neurologic Findings.—Right arm and leg weak, spastic, and atrophied; marked flexion deformity of right hand (claw hand) and arm; patient unable to extend the hand or grasp objects; Babinski on right with right hyperreflexia.

Laboratory Examination.—Negative.

Mental Examination.—I.Q., 59.

Encephalogram.—Relatively small skull, congenitally small sella, ventricular system well filled (no evidence of porencephay).

Operation.—A generous left mid-parietal bone flap was turned up in the usual manner and the dura opened widely. This revealed a huge accumulation of cerebral spinal fluid occupying the lower half of the parietal lobe and the greater part of the temporal lobe. There was almost complete atrophy of the cortex in this area. The cyst was drained and apparently communicated directly and completely with the ventricular system. I assumed that there was an agenesis and not a traumatic condition.

Course.—One year after operation the boy was more alert and making progress rapidly. Patient had advanced from first to second grade this year. He had only three convulsive attacks; in one he fainted and the others were indicated by jerking of arms and legs. There was some improvement of the motor defect according to his mother.

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THE TREATMENT OF COMMUNICATING HYDROCEPHALUS

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THE results of treatment of hydrocephalus in children have been so unsatisfactory that most parents are advised against interference. Bucy,[1] in a recent contribution on the subject, concluded: "It is to be regretted that such extreme pessimism is warranted in connection with the surgical treatment of hydrocephalus, yet such is the case. At the present time even the best-intentioned surgery can hardly serve other than to deny to some few cases the possibility of a spontaneous recovery by subjecting them to an operation and a surgical death."

Scarff[2] has recently revived interest in the surgical treatment of hydrocephalus by reporting on a comparatively large series of cases treated by destruction of the choroid plexus. He has improved upon the techniques of Dandy[3] and of Putnam[4] and stimulates a new optimism. Scarff did forty-eight operations on twenty children and reported a mortality of 15 per cent. The results are reported as satisfactory in ten children, or in 50 per cent of the cases, and as unsatisfactory in 35 per cent. About 20 per cent of the original group developed with a normal mentality.

It is my purpose in this report to direct attention to a simple and safe surgical treatment of hydrocephalus proposed by Hiller in 1933.[5] My series of cases is small, but it has been followed a sufficiently long time to permit of an evaluation of the procedure.

Hiller suggested the insertion of a waxed silk seton into the lumbar spinal canal with one end buried in the adjacent subcutaneous tissue. To facilitate the introduction of the seton Hiller described a simple modification of a standard spinal puncture needle. The hub of a 17-gauge spinal needle is heated and slid down the shaft of the needle just far enough to leave the proximal end of the shaft level with the top of the hub. The top of the stylet is bored to accommodate the portion of the shaft which then extends out. A No. 9 tonsil wire twice the length of the needle is added. A length of No. 1 well-waxed silk completes the equipment.

I have modified the needle by widening the proximal end of the shaft into a funnel shape. I have also marked the wire to indicate when the tip is level with the tip of the needle. The tip of the wire has also been made slightly bulbous and the distal end roughened with a cross to hold the knot better.

With the equipment sterilized the patient is prepared in the usual manner. The spinal needle is inserted with the child under local or general anesthesia. The excess fluid is allowed to drain slowly. The knotted end of the waxed silk thread is then introduced into the lumen

of the needle and is started with the stylet. The wire is then introduced and the knot is pushed through the needle into the spinal subarachnoid space. With the proximal end of the thread free, the needle is withdrawn holding the wire in place. Next, the wire is pulled out leaving the knot and the seton in place. The proximal end of the seton is now cut off at the skin level, and the skin is moved over the cut end of the thread. The patient is kept in bed with his head elevated for twenty-four hours.

PATIENTS TREATED

In 1935 I became interested in Hiller's suggestion and treated my first patient (Case 1). The results were satisfactory, and four more patients have now been similarly treated. A brief résumé of these cases is appended. There has been no mortality, no secondary infection, and the results have been uniformly good. Two patients have had one seton each, one patient has had two, and two patients have had seven setons. The two patients who have required multiple setons developed recurrences of hydrocephalus following falls on the head. Apparently the injuries were sufficient to disturb the delicate balance or equilibrium provided by the seton drainage. It is quite possible that the setons became encased and had ceased to function.

COMMENT

In any report of treatment of hydrocephalus it must be fully realized that some patients make spontaneous recoveries. I am quite aware of this fact and have seen cases of arrested development in hydrocephalus. However, the complete control of recurrences in two of the patients reported with the insertion of new setons demonstrates the value and effectiveness of the technique described. One patient has been kept under observation for seven years, one six years, one four years, one two years, and one six months. All of the patients were thoroughly studied before operation. This study included spinal and ventricle punctures. The injection of dye into the ventricles and a study of the dye absorption and excretion into the urine were done.

SUMMARY

A simple technique is described for the treatment of communicating hydrocephalus in children. The procedure consists in the introduction of a waxed silk seton into the cerebrospinal subarachnoid space with the proximal end of the seton buried under the skin. The method is simple and free of objections. Additional setons may be introduced whenever indicated. A simple needle is described to facilitate the introduction of the seton. In a series of five cases there has been no mortality and no secondary infection.

CASE REPORTS

CASE 1.—F. J. (M.C.H. 36761), an 8-month-old infant, was admitted to Milwaukee Children's Hospital Nov. 4, 1935. He had been well until two weeks before

when he awakened, held his head, and screamed. One week later he became blind. This was the mother's first pregnancy and the infant was delivered by forceps after a long difficult labor. There was resulting skull fracture and lacerations of the scalp.

Examination.—Multiple healed scars on the forehead and scalp. Head large, circumference, 47.5 cm.; chest, 45 cm.; anterior fontanel, 3 by 4 cm., tense. The pupils were dilated and did not react to light, and there was apparently no vision. The sclerae showed well above the pupils. Both optic discs were pale and edematous. The spinal and ventricular punctures revealed clear fluid under increased pressure. Phenolsulphonphthalein injected into the lateral ventricles was observed in the lumbar fluid within fifteen minutes. Daily spinal punctures were done until November 20 when the patient's vision had completely returned. On Nov. 22, 1935, a seton was inserted into the lumbar space and the patient was discharged Nov. 26, 1935. He was seen Dec. 6, 1935, when his head circumference was 49 cm. and his vision good. He was readmitted April 7, 1936, because of restlessness and sleeplessness. His head measured 50 cm., and Macewen's sign was positive. There was some strabismus. The spinal fluid was under increased pressure. It was drained off and a second seton was inserted. On Oct. 11, 1936, the symptoms had recurred and the patient was readmitted. The head circumference was 54 cm. The spinal fluid was under increased pressure; 75 c.c. were drained off and a third seton was inserted. On Sept. 10, 1937, he had a cold and otitis media on the right side. The membrana tympani was incised Sept. 13, 1937; he had a bulging fontanel. Head circumference, 57 cm.; chest, 53 cm.; spinal fluid under increased pressure. The fluid was drained off and a seton inserted. On May 17, 1938, he fell and struck his forehead on concrete walk. Examination revealed a large hematoma on the forehead. Spinal fluid was under increased pressure and ground glass in appearance containing many red blood cells. X-ray showed a fracture of the right frontal bone extending up 4 cm. from the orbit. He made a complete recovery. On Aug. 21, 1938, he fell and struck his forehead. He had a severe frontal headache, vomiting, and fever, On Aug. 28, 1938, the head circumference was 58.5 cm., and Macewen's sign was positive. Spinal fluid was under increased pressure. The fluid was drained off and a seton inserted. On Sept. 18, 1938, he fell and struck his head. He then had severe frontal headaches, nausea, and vomiting. On Sept. 20, 1938, the head circumference was 59 cm. The spinal fluid was under increased pressure. It was drained off and a seton was inserted. On Feb. 19, 1940, the child had had an occasional attack of vomiting and had developed an unsteady gait. Examination revealed a precocious mental development and adiadokokinesis. The head circumference was 61.5 cm. The scalp veins were not prominent. Spinal fluid was under increased pressure, and 76 c.c. were removed. On Feb. 23, 1940, a seton was inserted.

On Aug. 5, 1941, the child weighed 65 pounds and measured 45 inches in height. His gait was slightly unsteady and he had some adiadokokinesis. His blood pressure was 112/80. His mental development had been precocious. Head circumference, 63.5 cm.; chest, 65 cm.; abdomen, 65 cm. Aug. 18, 1942—child had been well. His weight was 69 pounds; height, 47 inches; head circumference, 63 cm.; chest, 69 cm.; abdomen, 67 cm. The gait was unsteady, but the child had not fallen. The mentality was excellent. The head circumference had not increased for one year; previously it had increased only 1.5 cm. in two years.

CASE 2—J. B. (M.C.H. 42534), an 8-month-old infant, was admitted to the Milwaukee Children's Hospital Aug. 23, 1938. She had apparently had meningitis one month before and had three attacks of "arching of the back" following. The mother also noted a marked increase in the size of the head in the month preceding admission. Examination revealed a large head, circumference of 51 cm., with large, dilated scalp veins. The sclerae were visible above the pupils. The spinal

fluid was under increased pressure but otherwise normal. Phenolsulphonphthalein was injected into the right ventricle. There was no dye recovered in the lumbar spinal fluid in one hour. Only 10 per cent of the dye was recevered in the urine in nine hours. On Aug. 26, 1938, no dye was recovered in the cisternal fluid. On Sept. 1, 1938, a lumbar spinal puncture was done. The fluid was clear but under increased pressure. Pressure applied to the anterior fontanel was transmitted to the lumbar needle. On Sept. 2, 1938, the spinal fluid was drained off through a lumbar puncture and a seton was inserted. On Oct. 3, 1938, the child had a stiff back. Examination revealed an increased area of sclerae visible above the pupils. The anterior fontanel was bulging. Macewen's sign was positive. The head circumference was 51.2 cm. On Oct. 26, 1938, another seton was inserted. On Nov. 28, 1938, the child was progressing normally. The head circumference was 53 cm.; chest, 45 cm.; abdomen, 45 cm. There was no increased tension over the anterior fontanel. On Jan. 23, 1939, the head circumference was 53.5 cm.; chest, 45 cm.; abdomen, 45 cm. Normal development; no symptoms. March 2, 1939—For the past few days the child had been listless and whining. The head circumference was 54.3 cm.; there was increased tension over the anterior fontanel. The right side of the head was larger than the left. A subdural tap in the right angle of the anterior fontanel revealed a ground glass fluid under no increased pressure; 28 c.c. were removed. Spinal puncture revealed a clear fluid under no increased pressure; 15 c.c. were removed. Pressure on the anterior fontanel was transmitted to the lumbar needle. On Mar. 3, 1939, there was a reaccumulation of the subdural fluid, and 60 c.c. were removed. On March 9, 1939, 40 c.c. of clear spinal fluid were drained off and a seton inserted. Head circumference was 53.2 cm. On Dec. 25, 1939, the child pulled a chair over on her head. Since then she had been fussy and held her head. On Dec. 29, 1939, the head circumference was 58 cm. Spinal puncture revealed a clear fluid under greatly increased pressure; 35 c.c. were drained and a seton was inserted. On March 25, 1942, the child was well and making a normal development until past few weeks when she would scream and hold the back of her neck. She complained of some stiffness of her legs. The head circumference was 61 cm., and there was a positive Macewen's sign. On March 27, 1942, the spinal fluid was clear, under increased pressure. It was drained off and a seton was inserted. On Aug. 13, 1942, the child was well and had made a normal development. The head circumference was 60.5 cm.; chest, 59 cm.; and abdomen, 60 cm. There was no Macewen sign and no other sign of increased intracranial pressure. On March 23, 1943, the head circumference was 62 cm.

CASE 3.—J. H. (M.C.H. 38821), a 4-month-old infant, was admitted to Milwaukee Children's Hospital Nov. 9, 1936. She had had a large head since birth; it had increased four inches in circumference in four months. On examination the head circumference was 65 cm. The anterior fontanel was large and bulging. Right ventricle puncture revealed a clear fluid under slightly increased pressure. The fluid was normal. Phenolsulphonphthalein injected appeared in the lumbar canal in eight minutes, and traces of the dye were recovered in the urine in twelve hours. Pressure on the anterior fontanel was transmitted to the lumbar needle. On Nov. 13, 1936, the spinal fluid was drained off and a seton was inserted. The head circumference was then 55 cm. By Dec. 29, 1936, the head had increased 1.5 cm. in circumference. A second seton was inserted. This infant was taken home (Michigan) and was said to be doing well for five months. At that time she developed "flu," then pneumonia, and died.

CASE 4.—J. H. (M.C.H. 47121), a 10-day-old infant, was admitted to the Milwaukee Children's Hospital Aug. 3, 1940. When the baby was 4 days old he had twitching of the upper extremities and a spastic convulsion. There was no bulging of the anterior fontanel. The spinal fluid was clear and normal. A subdural tap

yielded no fluid. Two days later nystagmus and projectile vomiting developed. Three days later there was increased tension over the anterior fontanel. The head was large, circumference 40 cm., and the sclerae showed prominently above the pupils. Chest circumference was 34.5 cm.; abdomen, 34.5 cm. Phenolsulphonphthalein injected into the right ventricle was recovered in the lumbar canal in five minutes; 30 per cent of the dye was recovered in the urine in twelve hours. The infant developed gradually increasing tension over the anterior fontanel but was discharged Aug. 11, 1940. He was readmitted Aug. 19, 1940. The head circumference was 42 cm., and there was considerable tension over the anterior fontanel. The spinal fluid was clear and flowed freely. It was drained. The infant was readmitted April 25, 1941, because of increasing size of the head. The infant had made a normal development. The sclerae showed prominently above the pupils; the head was large, circumference 53.75 cm. The chest circumference was 43.25 cm. The spinal fluid was clear and normal, but under increased pressure. Pressure on the anterior fontanel was transmitted to the lumbar needle. Thirty cubic centimeters of fluid were drained off, and a seton was inserted. From this time to July 10, 1942 (twenty-seven months), the child made a normal development and his head circumference increased 4.25 cm. while his chest increased 3 cm. and his abdomen decreased 1 cm. The anterior fontanel decreased from 5 by 7.5 cm. to 4 by 5 cm. The eyes looked normal. The child walked well.

CASE 5.—T. H. (M.C.H. 51243), an 11-month-old infant, was admitted to Milwaukee Children's Hospital Aug. 13, 1942. The birth history was normal. He had been slow in his development and had always had a large head. He could not sit or stand. The head was large, circumference 42.5 cm., and the scalp veins were prominent. The anterior fontanel was tense. The chest circumference was 41 cm.; abdomen, 36 cm. On Aug. 17, 1942, spinal puncture revealed clear fluid which was normal and under no increased pressure. On Aug. 18, 1942, ventricular puncture revealed clear fluid under no increased pressure. Phenolsulphonphthalein was injected and only a trace noted in the lumbar fluid in twenty minutes; 40 per cent of the dye was recovered in the urine in twelve hours. On Aug. 20, 1942, lumbar puncture was done; 20 c.c. of fluid were drained off and a seton inserted. On March 24, 1943, the infant was examined and had no evident increased intracranial pressure. Skull circumference was 48.8 cm.

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GLOMERULAR DEVELOPMENT IN THE KIDNEY AS AN INDEX OF FETAL MATURITY

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THE stage of bodily development which is attained before birth varies greatly among different mammalian species, but before being born each fetus must attain a state of development commensurate with the demands which will be placed upon it immediately after birth. Prior to birth all fetuses lead a protected, parasitic life, and little is required of them except that their constituent cells be able to multiply and differentiate. Anatomic and physiologic development are so integrated that progression of one is invariably associated with equivalent elaboration of the other.

The human fetus must ordinarily cope with the exigencies of extrauterine life in approximately 268 days after conception, or, as generally calculated, 280 days after the first day of the menstrual period which immediately preceded pregnancy. There is some variation in this length of time, but over 75 per cent of all infants are delivered within two weeks of the expected date.

The average birth weight of all infants exclusive of twins is in excess of 3,000 Gm. At the Chicago Lying-in Hospital the average weight of 4,000 unselected infants was between 3,300 and 3,400 Gm. Some variation has been found in different parts of the world, but in practically all studies where live infants were weighed the average is between 3,100 and 3,500 Gm.

The average normal human fetus thus appears to attain a weight between 3,000 and 3,500 Gm. in approximately 280 days from the first day of the last menstrual period and to have, by this time, acquired the ability to control its own body processes in the extrauterine environment to which it is ordinarily exposed. The fetus is mature and capable of undertaking a new mode of life.

The question arises as to how long the average fetus may be considered "mature" before delivery actually takes place. We know that prior to the expiration of twenty-eight weeks, the infant almost invariably dies soon after birth because of incomplete development. The body weight at the end of the twenty-eighth week averages about 1,000 Gm. Further growth gradually improves the ability of the various organs to function, and the fetus gradually becomes able to exist independently. Why premature infants of equal weights that are born of apparently healthy mothers and subjected to the same care after birth vary in their ability to survive is unknown. One may postulate that the intrauterine environment is not adequate in all, even if deviations from the normal

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cannot be demonstrated, and that consequently some babies are more handicapped than others at birth, or that labor and delivery produce varying amounts of injury, even when visible changes are absent; one may go even further and believe that in some instances the original genes with which the zygote is endowed lack some quality necessary to maintain life.

Almost all definitely premature infants appear to be subject to a greater hazard after birth than those who are generally considered mature. Difficulty is often encountered, however, in attempting to determine whether an infant should be considered premature or mature and in knowing how much it can vary from the average in size and length of gestation and still not be subject to unusual risks after birth because of inadequate development. The lack of agreement among investigators regarding physiologic measurements as criteria of maturity bears witness to this difficulty. The various methods recommended have been based on weight, sitting height, standing height, and age as calculated by absence of maternal menses, head circumference, relation between head and chest circumference, relation between fronto-occipital diameter and shoulder width. Other criteria suggested include the presence of certain ossification centers in the skeleton, size of the liver, length of the hair and nails, development of the placenta and cord, and the proportion of nucleated red blood cells to leucocytes in the peripheral blood.

The figures for determination of maturity are all based on averages and if an individual infant fails to attain the average level, it is generally considered premature. None of these criteria tells us actually how long the infant may be considered mature (if at all) before it is delivered.

Some fetuses grow faster in utero than others. Although with increasing birth weight the average length of gestation is found to be slightly longer, high birth weight and prolonged gestation are by no means necessarily found together. It has been observed clinically that babies weighing over 2,500 Gm. generally fare better than those weighing less. After this birth weight is attained, however, a greater weight does not appear to benefit the infant greatly.

Several questions present themselves. Is a baby which would have weighed 3,500 Gm. had it been delivered at 280 days but which weighs only 2,500 Gm., being delivered at 260 days, less mature and less able to function in an extrauterine environment than one which is delivered at 280 days with a birth weight at that time of 2,500 Gm.? Is physiologic development a corollary of weight or of gestational age? If one fetus grows more rapidly than another, is it more rapidly developing the ability to live independently; or are some large babies as immature as others who are of equivalent gestational age but much smaller in size? Is there justification for the attempted differentiation between

premature and immature babies, the first being a small baby of short gestational life, the second a small baby of average gestational life, and for the often accepted belief that the "immature" baby has a much better chance of survival than the "premature" on the basis of greater physiologic differentiation even in the absence of an average body weight?

In this paper an attempt will be made to answer some of these questions on the basis of the development of the fetal kidney, a subject in which we have been interested for some time. Our investigations have been especially concerned with development of the kidney glomeruli in relation to weight, length, the gestational age at birth, and to the length of survival of premature infants after birth. We believe that glomerular development may serve as an index to answer some of the questions just raised.

All structures in the body show a gradual elaboration of cellular pattern during the course of fetal life, and from the histologic examination of almost any organ it is possible to tell the approximate age of the fetus. The changes are more marked and an estimation of age is more easily made in the earlier than in the later stages of development. During the last two months it is the most difficult, for by this time the only change in the majority of the organs is one of continued growth, the pattern already having been established.

Some organs show a type of growth which is directly continuous after birth with no change punctuating the moment of changed environment (pancreas, thymus, etc.); others show uniform growth regardless of the size attained by the fetus as long as it remains within the uterus but undergo an abrupt change as soon as birth takes place, even if the fetus is delivered very prematurely (liver, suprarenal gland, etc.). During the last six weeks of fetal life the lung undergoes very little histologic change and from microscopic examination it is generally impossible to differentiate the lung of a 2,000 Gm. fetus from one weighing 3,000 Gm. The pattern changes immediately after birth and, although the question is not entirely settled, the differences which are visible appear to be purely mechanical and due to distension of the alveoli by air. The kidney is a unique organ whose growth is independent of environment but one in which a definite visible change occurs when the total potential number of glomeruli has been produced, regardless of whether the fetus is still within the uterine cavity or whether it has established an independent life.

It may not be amiss to sketch briefly a few of the broad features of kidney development. The glomeruli arise from a condensation of mesoderm known as the metanephric blastema which is present around the terminal portions of the growing branches of the metanephric bud. Each of the two metanephric buds arises as an outgrowth from the Wolffian duct of its appropriate side; each, by continued branching,

eventually produces a ureter, a kidney pelvis, and a collecting tubule. Each collecting tubule gives rise to successive generations of dichotomous branches. Around the tip of each of these latter branches the mesoderm in the vicinity condenses, develops a central cavity, and becomes S-shaped in form. One end of the S coalesces with the terminal portion of the collecting tubule and a continuous channel results. The proximal portion develops into the distal and proximal convoluted tubules and the loop of Henle; the distal end becomes the glomerulus and Bowman's capsule. The undifferentiated mesoderm and the immature glomeruli are readily visible on microscopic examination.

A marked divergence of opinion concerning the time when the production of glomeruli ceases is to be found in the work of different investigators. Peter[1] (1927) states that no new glomeruli are found after the eighth month of fetal life. Tsuda[2] (1934) believes that layers of new glomeruli form until the tenth lunar month of intrauterine life. Arey[3] (1934) says that all glomerular development terminates at birth. Maximow and Bloom[4] (1941) report that the production of new glomeruli "continues throughout the latter period of intrauterine life and comes to its end six or eight days after birth." Felix,[5] in Keibel and Mall (1912), makes the statement that, "The formation of uriniferous tubules (portions of which become glomeruli) is not completed at the close of the fetal period, but extends into the first days of extrauterine life. It is only after the tenth day that the formation of new tubules ceases, the neogenic zone exhausts itself in the formation of the last generation and vanishes." Jordan and Kindred[6] (1942) quote Toldt and Hauch as saying that "by the third month (after birth) the final generation may be present."

The study which we have undertaken deals with the cessation of new glomerular development in relation to fetal weight, length, gestational age, and survival after birth. The material chosen consists of histologic preparations of kidneys from 1,000 dead fetuses and infants who were examined at autopsy. They are consecutive and unselected except that the kidneys of infants who were malformed or macerated were excluded. If any incompletely developed glomeruli* were visible, the nephrogenic zone was considered as being present; if none were being formed, it was considered absent. There were 569 in which the zone was present; of these, 228 were stillborn, 245 lived less than twenty-four hours after birth, and sixty-nine lived from 2 to 69 days. There were 431 in which the zone was absent; 270 were stillborn, eighty-three lived less than twenty-four hours, sixty-eight lived from two to thirty-eight days.

Fig. 1 shows the total number of cases listed according to body length. With one exception (Case 8) all infants measuring less than 46 cm. have

*Increase in glomerular size and some elaboration of finer structural detail appears to take place after birth. Complete glomerular development, as the words are used in this paper, means a glomerulus which is a localized tuftlike structure and which has entirely lost the flattened character associated with its initial appearance.

new glomeruli developing, and with one exception (Case 1) no infant measuring 49 cm. or more shows the presence of immature glomeruli. In approximately one-half of the infants of 47 (to 47.9) cm., the production of glomeruli has ceased; in the majority of infants measuring less than this, they are still forming; in the majority measuring more, they are absent.

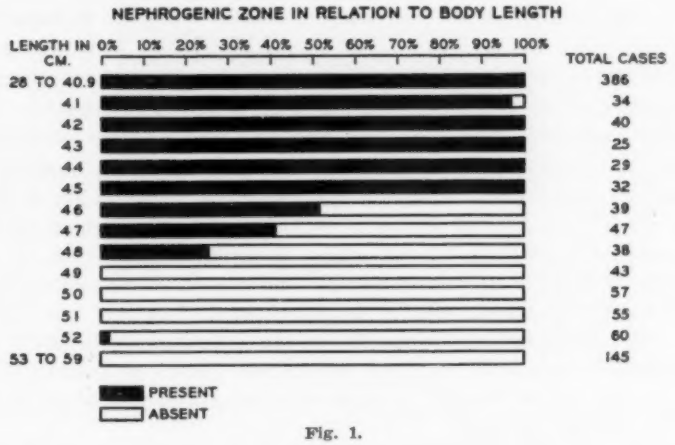

Fig. 1.

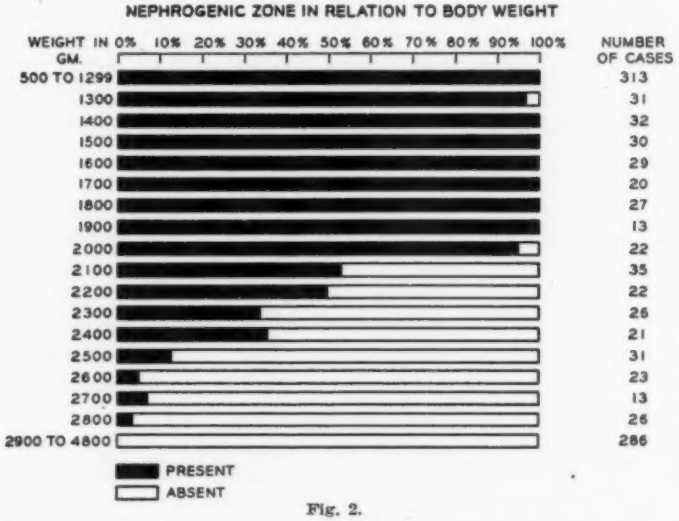

Fig. 2.

Fig. 2 shows the total number of cases listed according to body weight. (These are weights which were taken at autopsy and are consequently slightly lower than they would have been had the infants been weighed

while alive.) With only two exceptions (Cases 8 and 9) no infant weighing less than 2,100 Gm. failed to exhibit developing glomeruli; with seven exceptions (Cases 1 through 7) no infant weighing 2,500 Gm. or over showed developing glomeruli. Maturity of the kidney, as far as the production of new glomeruli is concerned, is almost always attained during the time that the fetus or infant weighs between 2,100 and 2,500 Gm. and measures from 46 to 48.9 cm.

The cases which show outstanding deviations from the average findings in Figs. 1 and 2 deserve some special comment. Although, as indicated subsequently, we believe that kidney development in general is much more closely related to fetal size than to length of gestation, these few cases appear, for the most part, to be exceptions to this conclusion.

Except in one case, all of those showing presence of the nephrogenic zone when the weight is in excess of 2,500 grams or the length is in excess of 48.9 cm. have a period of gestation which is compatible with the continued presence of the zone. It would suggest that in rare instances kidney development may not progress in direct proportion to body weight but instead may be dependent on the length of intrauterine life. In only one case (Case 9) in the entire series in which the nephrogenic zone is present are weight and period of gestation both beyond the average range. Even here the length of the infant is compatible with its presence.

The two cases showing absence of the nephrogenic zone in infants of low weight are in both instances associated with a length of gestation compatible with its absence. In Case 8 the fetus was a twin. The surviving twin weighed 2,375 Gm. and measured 47 cm. in length. Listed below are the nine outstanding cases in which glomerular development was other than would have been expected in relation to fetal length and weight:

	WEIGHT (GM.)	LENGTH (CM.)	GESTATION (DAYS)
	NEPHROGENIC ZONE PRESENT		
1.	2,710	52.0	248
2.	2,866	48.0	237
3.	2,645	48.7	245
4.	2,560	46.0	238
5.	2,530	48.5	249
6.	2,510	48.0	232
7.	2,585	47.5	278
	NEPHROGENIC ZONE ABSENT		
8.	1,320	41.8	252
9.	2,090	50.0	250

In Fig. 3 the presence and absence of developing glomeruli is shown in relation to the length of gestation. There is a much wider scatter than in Figs. 1 and 2 and instances where glomeruli are absent and others where they are present are found in the span from the beginning

of the thirtieth to the end of the forty-second week. However, the majority of infants show new glomerular development up to the beginning of the thirty-fifth week and fail to show it after this time.

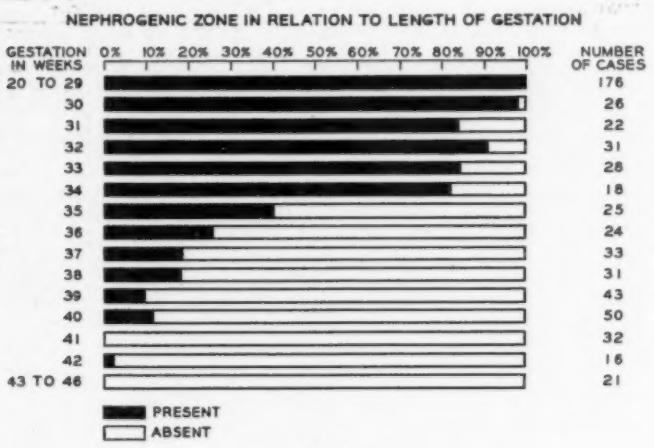

Fig. 3.

Table I indicates the average fetal weight in relation to the length of gestation in the groups where the nephrogenic zone is absent and present. At the same recorded gestational age, the average weight of those infants showing persistence of the nephrogenic zone is, in general, over 1,000 Gm. less than the weight of those in whom it is absent. Two possibilities arise to explain this fact; either the recorded lengths of gestation are in error or the development of new glomeruli in the kidney is more directly related to fetal size rather than to fetal age. In view of the number of cases in which a wide range of variation is found, the latter view would seem to be better supported than the former. Rare exceptions occur, as indicated in the cases cited previously.

There were ninety-six infants in whom glomeruli were still developing after survival from two to sixty-nine days following birth. All weighed less than 2,500 Gm. and measured less than 49 cm., and the period of gestation was less than thirty-eight weeks. There were sixty-eight infants who lived two or more days who failed to show developing glomeruli. The smallest of these weighed 2,110 Gm. and measured 46.7 cm. at the time of death, but all exceeded the minimal measurements which are found with absence of immature glomeruli. In Table II the data pertaining to the infants who still exhibited a nephrogenic zone is given. From this it is evident that the kidney continues its normal course of development into extrauterine life if delivery takes place prematurely—that the kidney fulfills its potential ability to produce glomeruli and is not hindered by the incident of birth.

TABLE I

AVERAGE BODY WEIGHT IN RELATION TO ABSENCE OR PRESENCE OF NEPHROGENIC ZONE ACCORDING TO LENGTH OF GESTATION

GESTATION (WK.)	NEPHROGENIC ZONE			
	ABSENT		PRESENT	
	NUMBER OF CASES	WEIGHT (GM.)	NUMBER OF CASES	WEIGHT (GM.)
20			5	791
21			3	783
22			7	716
23			10	707
24			19	846
25			23	809
26			27	887
27			19	960
28			26	1,052
29			37	1,294
30	1	2,370	25	1,338
31	4	2,355	18	1,363
32	3	2,820	28	1,710
33	5	2,986	23	1,885
34	3	3,315	15	1,766
35	15	2,802	10	2,002
36	18	2,809	6	1,896
37	27	2,962	6	1,903
38	25	3,022	6	1,872
39	40	3,842	3	1,910
40	45	3,404	5	2,065
41	32	2,940		
42	15	3,144	1	2,430
43	12	2,929		
44	3	3,400		
45	3	3,285		
46	3	3,725		

TABLE II

LENGTH OF SURVIVAL IN RELATION TO BIRTH MEASUREMENTS IN THIRTEEN INFANTS SHOWING PERSISTENCE OF THE NEPHROGENIC ZONE

WEIGHT (GM.)	LENGTH (CM.)	GESTATION (DAYS)	LIFE AFTER BIRTH (DAYS)	TOTAL LIFE (DAYS)
1,300	48.5	182	69	251
1,000	37.0	184	34	219
1,560	42.3	206	25	231
1,350	42.1	248	15	263
920	36.0	203	10	213
1,350	42.0	236	10	246
955	38.0	200	9	209
1,560	43.7	230	9	239
920	40.0	209	8	217
1,010	37.0	180	8	188
1,340	41.0	224	7	231
730	34.0	204	7	211
960	37.5	182	7	189

There were fifty-seven twins in this series of 1,000 infants. Of the fifty showing the presence of the nephrogenic zone, the heaviest infant weighed only 2,100 Gm.; of the seven in whom it was absent (except for Case 8 previously mentioned), one weighed 2,200 Gm. and the others

were in excess of 2,400 Gm. Twinning, in general, does not seem to alter the relation of kidney development to body weight.

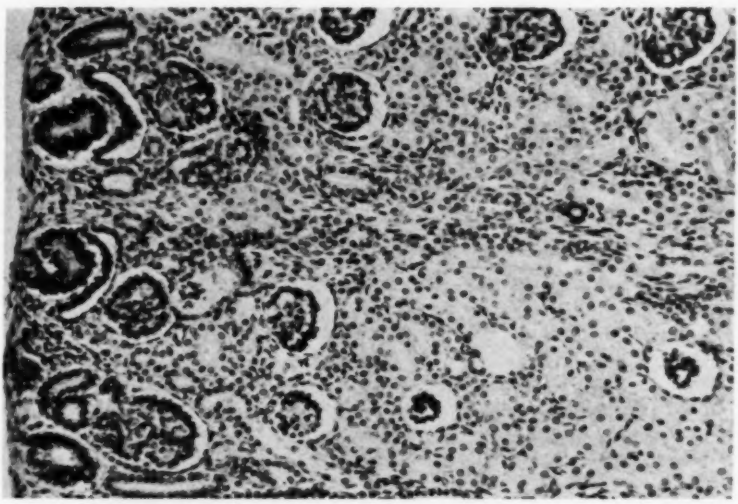

Fig. 5.

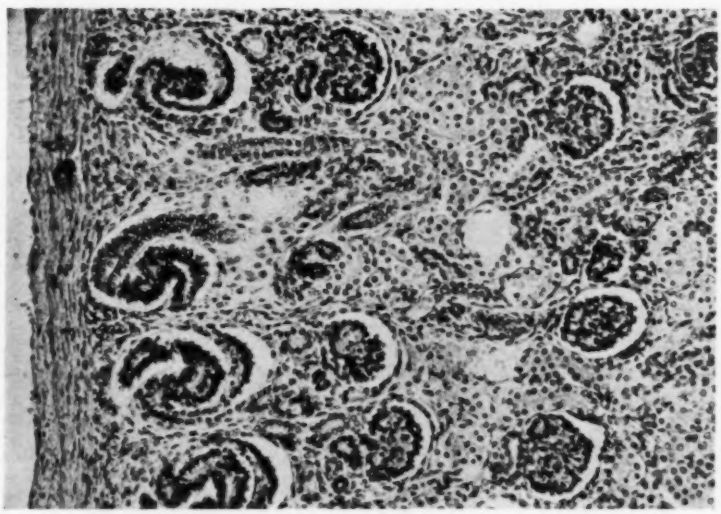

Fig. 4.

Fig. 4.—Subcapsular region of a kidney from an infant weighing 1,015 Gm. at birth; survival, eight hours. (×230.)
Fig. 5.—Subcapsular region of a kidney from an infant weighing 2,000 Gm. at birth; intrapartum death. (×275.)

DISCUSSION

From the material presented in this paper it seems clear that cessation of new glomerular formation in the kidney is not specifically related to the fact that birth has occurred but is, instead, dependent on the

size which the infant has attained at the time the examination of the kidneys is made. If birth takes place at the average time and the infant is of average size, glomerular production will have ceased prior to

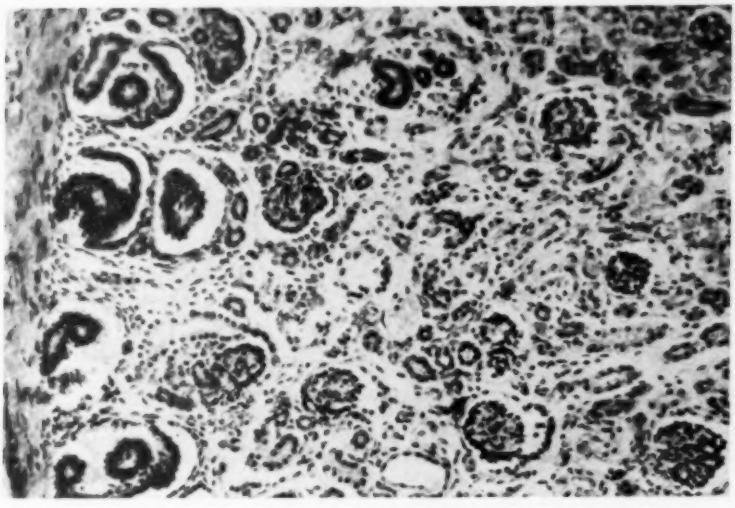

Fig. 7.

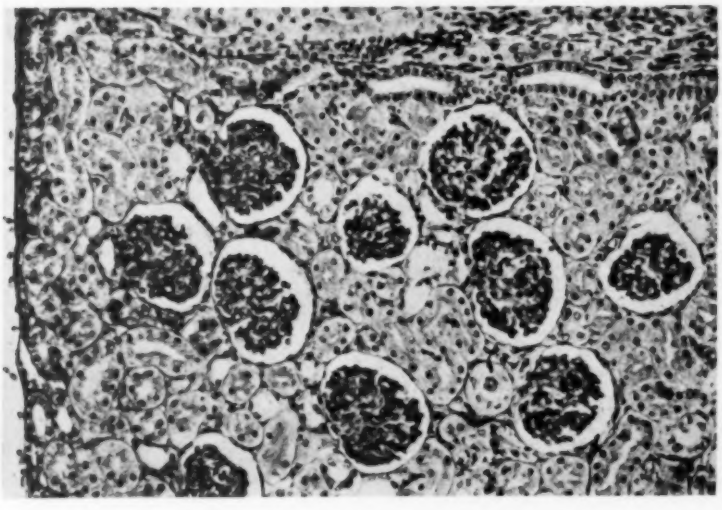

Fig. 6.

Fig. 6.—Subcapsular region of a kidney from an infant weighing 3,125 Gm. at birth; intraparium death. (×275.)
Fig. 7.—Subcapsular region of a kidney from an infant weighing 1,000 Gm. at the time of dea.h. Born at twenty-seven weeks of gestation and survived five weeks after birth. (×275.)

birth. If birth takes place before the expected date, the probability of continued glomerular production is dependent on the size of the fetus at the time of delivery. Glomerular development will cease when the potential number of glomeruli have been formed.

Glomerular production also seems much more closely related to fetal size than to gestational age. Regardless of the calculated gestational age, a fetus weighing less than 2,100 Gm. practically always shows glomeruli still being formed, one weighing over 2,500 Gm., practically never. If total body development—skeleton, muscle, fat—is slow in development, the kidney appears to be proportionately slow in maturing; if bodily development has been unusually rapid, the maturation of the kidney is hastened. This would seem to indicate that a differentiation between immaturity and prematurity is needless. Since the average weight of infants at birth is well over 3,000 Gm. and at the end of the thirty-sixth week is in excess of 2,500 Gm., it appears that, in general, the kidney is mature in relation to glomerular production at least one month prior to the time of delivery.

We believe consequently that glomerular development in the kidney forms an index of the maturity of the fetus. There is little visible evidence in other organs which can be used to mark the end point between the premature and the mature state. The completion of new glomerular formation marks an end stage which is very evident. It would seem that the resolution adopted by the American Academy of Pediatrics in 1935 to consider all infants weighing less than 2,500 Gm. as premature has an excellent basis in anatomic development as well as in clinical experience. According to our data, practically all infants weighing more than 2,500 Gm. at birth may be considered mature. An additional 50 per cent or more of those weighing from 2,200 to 2,500 Gm. are probably mature.

Nature appears ordinarily to allow a few extra weeks before birth takes place for increase in size and physiologic elaboration after anatomic differentiation is fairly complete.

CONCLUSIONS

Cessation of the production of new glomeruli in the kidney is primarily dependent on the size attained by the fetus and only secondarily on the gestational age.

Formation of new glomeruli ceases ordinarily when the fetus weighs between 2,100 and 2,500 Gm. and measures from 46.0 to 48.9 cm. in length.

The kidneys of the majority of fetuses born prior to the beginning of the thirty-fifth week (from the first day of the last menstrual period) show the presence of incompletely developed glomeruli; in the majority of those born after the beginning of the thirty-fifth week, none are visible.

The state of glomerular production constitutes an index of the maturity of the fetus.

Anatomic maturity of the fetus compatible with a normal adjustment to extrauterine life appears to be attained ordinarily at least one month prior to the usual time of birth.

In a prematurely born fetus glomerular production continues after birth until the potential number of glomeruli has been attained.

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SAFETY OF LARGE DOSES OF VITAMIN D IN THE PREVENTION AND TREATMENT OF RICKETS IN INFANCY

I. J. Wolf, M.D.
Paterson, N. J.

IT WAS shown experimentally in 1928 that rickets in the rat could be prevented and treated with single massive doses of vitamin D, one thousand times the daily effective dose.[1] It was not until some years later, however, when purer preparations of vitamin D became available that it was possible to use larger than normal amounts of vitamin D clinically without producing toxic effects. Large doses of vitamin D may now be safely given to infants for prolonged periods of time if deemed necessary, or single massive doses of vitamin D may be administered which may be repeated on occasional intervals.

The idea that large doses of vitamin D, without regard for other contributing factors, may be expected to cause calcification of the blood vessels and soft tissues has become firmly entrenched in the medical mind as the result of two series of events. First, in about 1929 following the use of old vigantol, a proprietary preparation of irradiated ergosterol, numerous clinical and experimental reports came out of Germany that this form of vitamin D was highly toxic and even fatal in larger doses. The exact doses used in terms of vitamin D units is not known, because this and similar preparations about this time differed not only in the potency of the irradiation product, but also in the concentration of vitamin D per cubic centimeter of the vehicle.[2]

Subsequently, as the result of the work of Holtz and Schreiber (1930), Göttche and Kellner (1931), Windaus, Luttringhaus, and Busse (1932), and Setz (1932),[3] it became known that the toxic and antirachitic effects of different irradiated ergosterol solutions did not run parallel and that the irradiation of ergosterol for short periods of time resulted chiefly in the production of tachysterol and calciferol,* whereas overirradiation produced toxisterol (Substance 248) and suprasterols, lacking in antirachitic action but strongly toxic.

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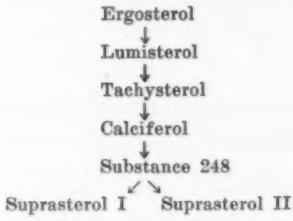
*Calciferol is vitamin D_2 and is available in pure crystalline form. The international unit (I.U.) of vitamin D, which is quantitatively the same as the U.S.P. unit, is equivalent to 0.000,025 mg., or 0.025 μg of crystalline calciferol. One milligram of calciferol is equivalent to 40,000 international or U.S.P. units of vitamin D. Vitamin D_3 is activated 7-dehydrocholesterol and is the chief form in which vitamin D is present in fish liver oils.

Viosterol is the nonproprietary name adopted by the Council on Pharmacy and Chemistry of the American Medical Association for all acceptable preparations of activated ergosterol. Under the best conditions of preparation, it is composed of approximately 50 per cent of calciferol, with lumisterol and tachysterol accounting for most of the remainder. It is standardized in terms of its vitamin D activity, so that the content of lumisterol and tachysterol, which have little or no antirachitic effect, are not taken into account.[3]



The old vigantol, according to the manufacturer's specifications, was required to be irradiated until toxisterol in maximum concentrations was produced; not vitamin D.

Shelling and Jackson[4] have pointed out that, "notwithstanding the fact that vigantol probably produced some toxic effects in human beings, it is equally true that many of the reports are groundless and the clinical and pathologic findings purporting to show its toxic effects are so slight and insignificant as to be in the realm of normal, or that they have no etiologic relation to vitamin D. For example, before the introduction of vitamin D, slight cellular infiltration of the wall of the kidney pelvis in a child suffering from chronic pyelitis would be looked upon as a natural and expected finding; yet as reports of toxicity of vigantol were forthcoming, such or similar findings assumed significance in the eyes of the investigators as signs of vitamin D poisoning."

Second, certain cases have been repeatedly quoted in the literature as cases of "vitamin D poisoning," erroneously labeled, without any critical review of the original case report on the part of the reviewer. A classic example of this is Thatcher's[5] often quoted fatal case of so-called hypervitaminosis D in an infant. At the age of 13 months this infant was started on a preparation of irradiated ergosterol emulsion, the potency of which was not stated. He received four teaspoonfuls of this emulsion daily from May until September, a dosage which the author states was twice the recommended curative dose. He was a feeding problem from birth and failed to gain weight from the age of 5 months, suffering from persistent digestive disturbances. In other words, some disease process was present long prior to the time he was started on irradiated ergosterol, which was given in doses not constituting vitamin D overdosage. Clinically this infant suffered from a pyelonephritis and at post-mortem the microscopic examination of the kidneys showed a deposition of calcium within the tubules of the kidneys as well as pus cells, evidence of a pyogenic infection.

Again in 1936 Thatcher[6] reported a case of so-called hypervitaminosis D in an infant aged 1½ years in whom calcium was found deposited in the kidney tubules on post-mortem examination. In addition, there were some small foci of mononuclear cells unrelated to the calcium deposits, some dilatation of groups of tubules which contained "colloid" casts, parenchymatous degeneration of the epithelium of the tubules in the

cortex, and slight edema of the stroma. There was no evidence of pyogenic renal infection. Vitamin D cannot be termed a factor in causing the metastatic calcification in this case inasmuch as minimal amounts of vitamin D were administered. The infant received one-half to one teaspoonful of cod-liver oil daily from June to the end of October, and on some days the oil was given three times a day.

Other cases in the literature in which vitamin D has been unjustly incriminated as the cause of metastatic calcification have been instances of severe renal disease, such as chronic interstitial nephritis, polycystic kidneys, hydronephrosis, or pyelonephritis. In such cases too small doses of vitamin D may lead to renal rickets, or, if larger doses of vitamin D are administered, doses which under ordinary circumstances are perfectly safe, metastatic calcification of the organs and blood vessels may follow. Experimental work in rats as well as clinical studies have shown the importance of renal damage on the toxicity of vitamin D.[7]

Karelitz and Kolomoyzeff,[8] in 1932, reported a case of chronic interstitial nephritis in a child, who at the age of 18 months developed renal rickets and who did not respond to ordinary doses of cod-liver oil (15 c.c. daily). At the age of 6 years healing was initiated after the administration of 7,000 R.U. of viosterol daily for six weeks, and later, about 5,000 R.U. daily for forty days. Hypercalcification of the arteries and intra-abdominal deposits of lime were shown on roentgenogram five months after the administration of the viosterol.

Shelling and Hopper,[9] in 1934, pointed out that patients with renal rickets usually have retention of phosphorus and are unable to excrete it in the urine. "In such cases, the constant transport of calcium phosphate in the blood in excess of its solubility may lead to metastatic calcification in the soft tissues, especially in the medial coats of the medium-sized arteries. Since vitamin D not only increases the calcium, but also the inorganic phosphorus in the serum, the injudicious use of vitamin D preparations may enhance the occurrence of abnormal calcification."

Andersen and Schlesinger,[10] in 1942, reported two cases of renal hyperparathyroidism with calcification of the arteries. The essential pathology on post-mortem examination was a severe renal anomaly, hypertrophy of the parathyroids, osteitis fibrosa, and metastatic calcification of the small arteries throughout the body. The first infant was 6 weeks of age on admission and weighed about 6 pounds. He received 10 drops of percomorphum liver oil daily, approximately 1,500 U.S.P. units of vitamin D, until the age of 3 months. After this 2 drops of vitamin D_2 in propylene glycol was given for six weeks (500 units per day). Eight drops of the same preparation (2,000 units daily) were administered from the age of 4½ months until death two months later. These doses, although not excessive, led to metastatic calcification as a result of the renal pathology.

The second infant was 4 weeks old when admitted with convulsions of one day's duration. On the day after admission he was given 300,000 U.S.P. units of vitamin D_2 (irradiated 7-dehydrocholesterol). Calcium was administered by mouth and intramuscularly. He received no further vitamin D therapy until he was 3½ months old. At this time he received 6 to 8 drops of viosterol in oil daily for one week, after which the dose was increased to 15 drops. This dose was continued until death at 6 months of age. The pathology on post-mortem examination was similar to the first case. These doses of vitamin D, although larger than ordinarily used, are well tolerated normally and do not lead to metastatic calcification. The presence of renal pathology was the predisposing factor.

Calcification of the arteries and organs may occur in infants as the result of disturbances of calcium metabolism in which vitamin D is not a factor. Kidney disease is usually present. Hild[11] recently reported calcification of the arteries, and deposits of calcium in both lungs in an infant with renal insufficiency who received subminimal doses of vitamin D. Baggenstoss and Keith[12] reported the case of an 8-week-old female infant who received no vitamin D and showed extensive calcification of the arteries, heart, and kidneys. He reviewed nine other similar cases from the literature, making no mention of vitamin D, in four of whom kidney disease was present.

FACTORS RESPONSIBLE FOR VITAMIN D TOXICITY

The production of toxic effects with vitamin D depends upon a number of variable factors which have been recognized by authorities such as Bills, Shelling, Reed, Struck, and Steck, and others.[13] These factors may be enumerated as follows:

1. Dosage per units of body weight
2. Duration of administration
3. Calcium and phosphorus content of the diet
4. Vitamin A content of the diet
5. Age and activity of the subject
6. Species or individual susceptibility
7. Vehicle in which the vitamin is administered
8. Route of administration
9. State of alimentary tract
10. Functional state of endocrine system
11. Kidney function
12. Presence of rickets or resistant rickets
13. Source of vitamin D
14. Purity of the preparation
15. Other factors not yet recognized.

Infants with rickets tolerate larger doses of vitamin D than normal infants. If the rickets is refractory, massive doses are required to procure a therapeutic response. If renal disease is present, whether associated with rickets or not, larger doses of vitamin D may result

in metastatic calcification. Other factors which play a role in vitamin D toxicity may be discussed briefly. An increased phosphorus content of the diet may influence the toxicity of excessive doses of vitamin D. A ratio of phosphorus to calcium of 4.32 to 1 is necessary. Vitamin A deficiency may also influence the toxicity of vitamin D, and large doses of vitamin A may have a protective influence.

Vitamin D is thought to have some effect on the thyroid, parathyroid, anterior pituitary, and the thymus. Administration of vitamin D in milk seems to enhance its antirachitic effect, although the exact explanation of the mechanism is not clear. Parenteral administration of massive doses of vitamin D is probably more effective than enteral administration, but from a practical point of view, excellent clinical results are obtained when vitamin D is given in single massive doses orally, except in cases of poor intestinal absorption. There is some evidence to show that irradiated cholesterol is less toxic than irradiated ergosterol, but other evidence is contradictory.[14]

Clinically, the symptoms of vitamin D toxicity in infants and children are anorexia, loss of weight, weakness, thirst, and vomiting. Calcium casts may be present in the urine. The blood calcium and phosphorus levels are elevated, although the degree is no indication of the intensity of the intoxication. The blood content of vitamin D as estimated by biologic tests is elevated as shown by Warkany.[15] The normal vitamin D blood content is about 110 U.S.P. units per 100 c.c. of serum. In the rachitic patient large doses of vitamin D cause a rapid deposition of calcium at the metaphyses. In the normal subject prolonged administration may cause demineralization of the long bones.

Dosage in Relation to Toxicity.—In experimental animals, the range between therapeutic efficacy and toxicity is very great.[16] Rosenheim and Webster (1927), Harris and Moor (1928), Light, Miller, and Frey (1929), Collazo, Rubino, and Varela (1929), and Harris, Ross, and Bunker (1939) have placed the toxic level in animals on short-time feeding experiments between 5,000 and 100,000 times overdosage as lethal. In long-time feeding experiments in the rat, Bills and Wirick[17] showed that a dosage of 1,000 times that of the minimum rachitic level was just perceptibly harmful; 4,000 times overdosage of viosterol was definitely injurious; and 40,000 times overdosage was strongly toxic.

In the human subject as well as the experimental animal, toxic levels are reached in a shorter time if the daily doses are sufficiently large. If smaller massive doses are used, the high levels may be continued indefinitely. Adult human beings can tolerate enormous dosages. Rappaport and Reed (1933) and Reed (1934)[18] administered doses amounting to 2,760,000 I.U. daily for the treatment of hay fever and other ailments. Such an enormous daily dose, 920 times the ordinary therapeutic dose of irradiated ergosterol, was more than some individuals could tolerate with comfort, yet it produced no serious poisoning. Spies and Hanzal (1934)[18b] administered over 18,000,000 I.U. per day

for from nine to twenty-five days to patients about to die of disease (more than 6,000 times the ordinary amount), producing hypercalcemia but no pathologic calcification of the tissues at autopsy. Kerr[18b] reported a case of an obese physician, aged 74, with generalized arteriosclerosis who took by mistake 2,300,000 international units of vitamin D in the form of concentrated solution of viosterol, daily for eighteen days, or a total of more than 40,000,000 I.U. Nausea, anorexia, weakness, increased thirst and polyuria developed and finally he went into coma and died.

The age and weight of the subject has to be taken into consideration in administering massive doses of vitamin D. Steck, Deutsch, Reed, and Struck,[19] in experiments on dogs, showed that it was important to record data as to the dose per unit of body weight. Both human beings and dogs generally survive the administration of 20,000 units per kilogram per day of vitamin D for indefinite periods without intoxication. Levels beyond this are toxic.

In children moderately large doses of viosterol are well tolerated for long periods. In 1930, Hess, Poncher, Dale, and Klein,[20] using 600 and 1,000-D viosterol in twelve infants, six of whom were Negroes, showed that doses twenty-one to fifty-two times the prophylactic dose in long-time feeding periods (six to eight months) were not toxic to these infants. They also found that infants tolerated 250 times overdosage for short periods without toxicity. Shelling and Jackson[4] reported in 1934 that in five years' experience with standardized viosterol in fairly large doses (3,240 to 8,100 international units) for weeks or years, no manifest symptoms of viosterol poisoning were encountered. Necropsies on thirteen children on the above dosages for from twenty-three days to thirteen and one-half months failed to show toxicity in the soft tissues or in the skeleton.

The safety of single massive doses of vitamin D for the prevention or treatment of rickets in infants and children has been conclusively shown to be safe. Since 1929 Petenyi, Götteche, Harnapp, Schirmer, Bischoff, Windorfer, Vollmer, and Braulke[21] have treated rickets in infants with single massive doses of vitamin D ranging from 100,000 to 600,000 units. No evidence of toxicity has been reported. This method of therapy brings about rapid healing of the rachitic process. Since 1938, when Harnapp introduced the massive dose method for rickets prophylaxis, numerous authors have given infants from 200,000 to 600,000 units of vitamin D for this purpose. Harnapp, Windorfer, Brockmann, Schwartzer, Reitschel, Hartenstien, Heisler, Hofmeier, Zelson, and Wolf[22] have shown that from 400,000 to 600,000 units of vitamin D administered in one, or two divided doses, is capable of protecting infants, even premature infants, for several winter months from developing rickets. No evidence of toxicity has been reported. Zelson even administered 600,000 units of vitamin D to premature infants as young as 12 days of age for the prevention of rickets without ill effect.

Examination of the tissues of infants and children dying of other diseases, who received single massive doses of vitamin D (as high as two or three million units), has also shown the absence of toxic effects. In 1939 Vollmer[23] gave a 4-year-old Negro boy 600,000 units of vitamin D orally and 1,000,000 units of vitamin D in 1 c.c. of oil intramuscularly three and one-half days and thirty-six hours, respectively, before he died of miliary tuberculosis. No evidence of calcification of the tissues could be found. In 1941 he[24] gave a 3-year-old child, who eventually died of lymphatic leucemia, a total of 2,260,000 units of crystalline vitamin D_3 (200,000 units per kilogram) diluted in oil and ether and administered intramuscularly twenty-six, thirteen, and seven days before death. No evidence of tissue calcification was found. Another colored child, aged 19 months, who died of miliary tuberculosis, was given a total of 1,260,000 units of vitamin D (200,000 units per kilogram) in the form of fish liver oil concentrate without a solvent, intramuscularly, nine and then three days before death. No evidence of metastatic calcification was found in the blood vessels or organs.

Vitamin D Dosage in Refractory Rickets as Compared to Renal Rickets.—Cases of resistant or refractory rickets not due to renal disease require massive doses of vitamin D in order to produce a therapeutic response. As was pointed out, in renal rickets larger than normal doses of vitamin D may result in metastatic calcification. Gittleman and Pincus,[25] in 1942, reported a case of resistant rickets (De Toni-Fanconi type) in a child aged 4½ years, who showed a disturbance in the fat metabolism which resulted in ketosis, which in turn so interfered with the mechanism for concentrating phosphorus in the blood that orderly calcification was prevented. Vitamin D was administered in amounts as high as 3,000,000 units over a period of several weeks without effect on the phosphorus level in the blood.

An unusual report is given by McCune[14] who treated refractory rickets in identical twins. Rickets was first recognized at 18 months of age. Irregular treatment with cod-liver oil, viosterol, and summer sun failed to produce healing. Rickets was still present at the age of 9 years. The calcium serum was 10 mg. per cent and the serum phosphorus, 1.5 mg. per cent; phosphatase, 15 Bodansky units. Warkany reported 150 U.S.P. units of vitamin D per 100 c.c. in the blood. There was no evidence of kidney disease. These twins were treated daily for eight months with 50,000 units of calciferol in propylene glycol (a total of 12,000,000 units), effecting a transient rise of serum phosphorus to 3.5 mg. per cent and the serum vitamin D to 2,600 units per 100 c.c. of blood serum. The serum calcium was not affected, and no clear-cut evidence of roentgen healing was seen. At this point one twin was given irradiated 7-dehydrocholesterol, and the other remained on calciferol. The dose was increased rapidly each day to 480,000 units. In both cases consistent and equal increase of the serum calcium and phosphorus became apparent at the level of 120,000 units daily. Definite

healing on roentgen examination was not evident until the end of eleven days, during which time each child was receiving 480,000 units daily. At this time the urine was loaded with amorphous phosphates and calcium casts. The vitamin D in blood serum rose to 18,000 units per 100 c.c. The serum phosphorus was 4.5 mg. per cent, and the serum calcium in one twin was 12.2 mg. per cent and in the other, 13.4 mg. per cent on calciferol and irradiated cholesterol, respectively. Neither child complained of subjective disturbances. When treatment was discontinued the manifestations of vitamin D intoxication receded at equal rates in the two children.

Level at Which Vitamin D Is Toxic in Normal Infants and Children.—Even though one uses purified preparations of vitamin D, such as pure calciferol or irradiated 7-dehydrocholesterol, free from toxisterol or suprasterols, it is possible to produce toxic results in infants and children if sufficiently large doses are given for a period of time. The dose required of course depends on the age and weight of the infant, the mode of administration, the susceptibility of the patient, and the various other factors discussed. It is important to know, of course, at what levels toxic effects may be expected in the average infant free of rickets or renal disease. The literature, however, except for earlier unreliable reports, is remarkably free of such reports. Ross and Williams,[26] in 1939, reported a case of a premature twin between 8 and 14 months of age (a group of four cases were reported and no exact details were given) who received a preparation of irradiated ergosterol, containing no toxisterols, in daily doses of 20,000 to 40,000 U.S.P. units of vitamin D for several months, a total dosage of about 3,000,000 units. The symptoms that followed were anorexia, loss of weight, and vomiting. The infant died suddenly following a bronchopneumonia, and post-mortem examination of the tissues showed extensive metastatic calcification of the arteries, cardiac muscle, kidney tubules, stomach, and lungs. The other twin died, but no autopsy was performed. The two other patients recovered. One suffered from a pyelonephritis which was probably a factor in the production of vitamin D toxicity.

CASE REPORT

I wish to report a case of toxic, metastatic calcification of the kidney tubules in a young infant.

Baby M. was born on Feb. 11, 1942, presenting a spina bifida in the lumbosacral region and a meningo-myelocele. The head was enlarged, and there was a palsy of both legs. No operative procedure was instituted. This infant was given massive doses of vitamin D to determine his toxic level.

On March 7, 1942, he was started on daily doses of 300,000 U.S.P. units of an electrically activated ergosterol* for two weeks. The preparation was adminis-

*Ertron, Nutrition Research Laboratories, Chicago, Ill. In the manufacture of ertron, ergosterol is first heated in a partial vacuum until it is vaporized. While it is in a gaseous state, an electric current of controlled amperage and voltage is passed through it for a specific length of time. Being in a gaseous state, all of the ergosterol is exposed to exactly the same amount of activation. It is then bioassayed according to the U.S.P. method for vitamin D and diluted in a solid fat and other inert material.

tered in a nonirradiated evaporated milk formula and was retained except on three occasions. These were on March 10, when a very small amount of feeding was regurgitated; on March 11, when most of the feeding was vomited; and on March 16, when some of the feeding was regurgitated. On March 14 the baby had some watery stools. It is estimated that he retained about 3,500,000 units of vitamin D in the course of two weeks. During this time he suffered from an infection of the right scrotum and groin. This opened spontaneously and drained a purulent material. A culture on March 18 showed *Bacillus coli* and nonhemolyticus streptococci. Between March 3 and March 19 the temperature ranged between 100 and 104° F. The last two weeks of life the temperature remained at a subnormal level.

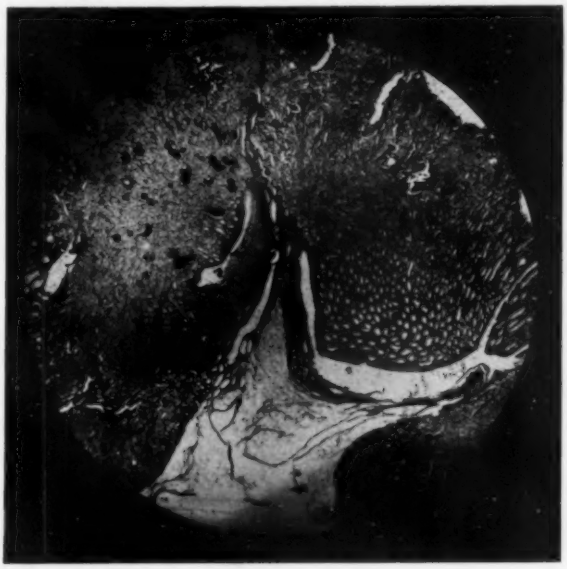


Fig. 1.—Section of kidney tissue under low power, showing numerous deposits of calcium in irregular, bluish-staining masses, especially in the tubules (hematoxylin-eosin stain).

The infant's birth weight was 9 pounds, 6 ounces. On March 2, prior to the massive vitamin D therapy, his weight was 8 pounds, 2 ounces. On March 18 his weight was 7 pounds, 2 ounces, and on April 25, his weight was 7 pounds.

A blood calcium and phosphorus taken on March 4 was 11.5 mg. per cent and 4.7 mg. per cent, respectively. On April 9 a Mazzini blood test was negative. A spinal fluid Wassermann on this date was also negative. On April 3 the total proteins in the spinal fluid was 435 mg. per cent. Unfortunately no other laboratory work was done.

No change in the infant's condition was seen following the massive vitamin D therapy. He fed as usual, the meningomyelocele showed signs of granulating, and the head enlarged to a circumference of fifteen and three-fourths inches. The scrotal infection subsided spontaneously. On May 1, 1942, during a diagnostic cisternal tap, the infant died suddenly. This was six weeks after the completion of two weeks of daily massive doses of vitamin D.

Pathologic Report (Dr. S. Gladstone).—The body was that of marasmic, hydrocephalic infant, aged 3½ months. The head was characteristically enlarged, and

the eyes were small and shrunken. The lower lumbar spine showed a defect in the spinal lamina with a protruding flat, oval mass six centimeters long. On opening the skull, the cerebral cortex was found to be edematous and thin and the ventricles markedly dilated and filled with clear, xanthochromic fluid. The thoracic and abdominal viscera appeared normal.

On microscopic examination of the organs, the brain showed numerous cell nuclei but a reduction in the amount of intercellular substance. The heart and great vessels appeared normal. The malpighian corpuscles of the spleen were numerous. The kidneys showed numerous deposits of calcium in irregular, bluish staining masses, especially in the tubules (Figs. 1 and 2).

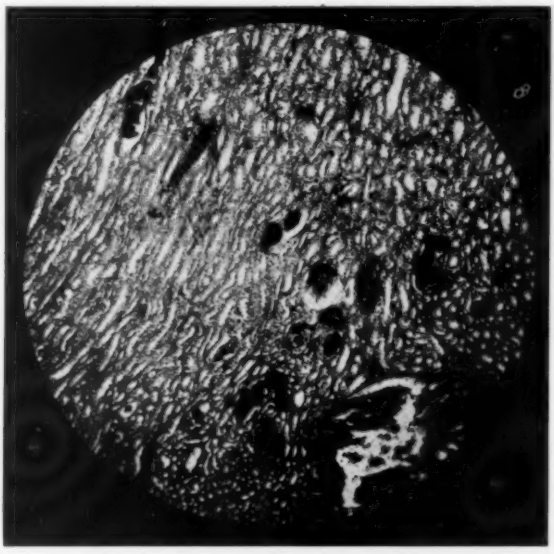


Fig. 2.—Same section under high power.

COMMENT AND SUMMARY

A male infant with a meningomyelocele, spina bifida, hydrocephalus, and palsy of the lower extremities, weighing 7½ pounds at the age of 1 month, was given 300,000 U.S.P. units of electrically activated ergosterol daily by mouth for fourteen days for the purpose of determining the toxic level of vitamin D. Two of these doses were not retained. It is estimated that he received a total of about 3,500,000 units in twelve consecutive days. During a cisternal tap performed six weeks later, at the age of 2 months and 3 weeks, he died suddenly in collapse. Microscopic examination of the kidneys showed considerable metastatic calcification of the tubules. No other organs or blood vessels were involved. Toxic manifestations were produced at a daily level of about 85,000 U.S.P. units of vitamin D per kilogram of body weight given for twelve consecutive days.

From a review of the literature it is apparent that there is a wide margin of safety in the use of large daily doses, or single massive doses, of vitamin D in infants and children. Numerous factors must be considered in evaluating the toxicity of vitamin D. An infant with rickets can tolerate larger doses and in refractory rickets not due to renal disease, it is necessary to use massive doses in order to bring about a therapeutic response. However, the presence of renal disease makes the infant more susceptible to vitamin D therapy, and doses which are ordinarily well tolerated may produce metastatic calcification.

The use of preparations of irradiated ergosterol which contain toxic irradiation products, such as toxisterol (Substance 248) renders the preparation more calcific. The early reports in the literature citing toxic effects with larger than normal doses of vitamin D followed the use of such preparations. Such reports, and reports of toxicity of vitamin D in the presence of renal disease, have led to the belief that larger doses of vitamin D may be expected to cause metastatic calcification in the soft tissues, without regard for numerous contributing factors, the significance of which have been stressed. Even disturbances of calcium metabolism in which vitamin D does not play a role possibly cause metastatic calcification.

However, purified preparations of irradiated ergosterol, if given in sufficiently large doses, may produce metastatic calcification. It has been shown that adults and experimental animals can tolerate 20,000 U.S.P. units of vitamin D per kilogram of body weight daily for indefinite periods. Doses beyond this level may be toxic.

In the case here reported, metastatic calcification of the kidney tubules was produced experimentally in an infant aged 3 months, weighing 7½ pounds, at a level of about 85,000 U.S.P. units of vitamin D per kilogram, given daily for twelve consecutive days.

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PHENOLPHTHALEIN TOLERANCE IN CHILDHOOD

An Analysis of Four Cases

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PHENOLPHTHALEIN has been used extensively as a laxative for both children and adults since its introduction by Vamossy in 1900. Its therapeutic importance is evidenced by its inclusion in the United States Pharmacopoeia and the National Formulary and its classification as "a useful drug" in the Epitome of the United States Pharmacopoeia and National Formulary, published by the American Medical Association. According to Beckman,[1] Fantus lists 28, and Belote and Whitney[2] report 102 laxative preparations in which it is one of the active ingredients. It is practically tasteless and odorless, is easily incorporated into candylike tablets, chewing gum, and certain types of liquid vehicles. Its use rarely produces abdominal discomfort. In one form or another, it is commonly found in the household medicine cabinet.

Clinical observation has established the fact that tolerance to the drug is almost universal and untoward sensitivity a rarity. Occasionally, so-called "fixed skin eruptions"[3] have been reported similar to those seen after the ingestion of many other drugs in common use. In a few instances, systemic reactions, coincident with the use of phenolphthalein, have been reported. However, none of these reports are accompanied by either laboratory or other supporting evidence from which it may be established that this drug is the causative agent of the reaction. Sollman[4] states that "very large doses have often been given without bad effects; to man, several grams by mouth"; and that "toxic effects in the use of phenolphthalein are exceptional." He mentions a case reported by Cleeves[5] in which the latter attributed a boy's death to his ingestion of 18 gr. of phenolphthalein. However, after a critical examination of Cleeves' report, Vamossy[6] (who did the original research work on the laxative effect of the drug) expresses the belief that this child's death was due to sepsis, and that the ingestion of phenolphthalein was only coincidental.

Our experience leads us to agree with the opinion expressed by most authors, that both sensitivity and unfavorable reaction are uncommon. We have observed the effects of repeated doses on a large number of children over a period of many months, incidental to an investigation for the purpose of establishing the optimal laxative dose for various age groups.[7] No instance of sensitivity or of unfavorable reaction occurred during the study, nor has any such instance come under the observation of one of us (M. L. B.) during thirty years of pediatric practice.

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In an effort made several years ago to ascertain the toxicity of the drug, Fantus and Dyniewicz[8] were unable to kill daphnia, worms, mice, cats, dogs, pigs, or monkeys with phenolphthalein administered in any dose; nor were there any untoward symptoms when large doses were given to patients with various diseases or to medical students who volunteered as test subjects. Fantus et al.,[9] in a subsequent research, found activated charcoal to be an adsorbent of the drug and suggested that the ingestion of an overdose of this laxative be followed by charcoal and later castor oil.

The United States Pharmacopoeia recommends a dose of 1 gr. but Beckman[1] states that "the adult dose is from 1 to 3 gr., though it is said that as much as 15 gr. may be given with safety."

It is our belief that Beckman's estimate is conservative. This opinion is supported by cases reported by Sachs[10] and Novince,* in which much larger doses were ingested with no ill effect, and by our recent observation of two children who had taken large amounts of phenolphthalein.

A study of the reports on these four cases shows that the laxative response to the drug bears little relationship to the child-adult weight ratio; for example, assuming 150 pounds as the average adult weight, a given dose of the drug does not act three times as forcefully when given to a child weighing 50 pounds. In common with most cathartics, its action is due to local stimulation and not to an effect following absorption. A fraction of ingested phenolphthalein is absorbed and may be demonstrated in the blood stream and in the urine as a conjugate product for several days after its ingestion, but the cathartic action bears no direct relation to the amount so absorbed.

CASE REPORTS

CASE 1.*—A well-nourished girl, 2½ years of age, was brought to the Cook County Hospital on Dec. 1, 1940, because two hours previously she had taken six tablets, each containing 2 gr. of phenolphthalein, a total of 12 gr.

On admission the child showed no ill effects. She was comfortable and cheerful. There was no fever, no flushing of the skin, nor any abnormal neurologic signs. The heart, lungs, and abdomen were normal. There were several old fingernail scratch marks over the upper and lower extremities and a slight infection of a scratch wound over the dorsum of the left little finger.

Laboratory findings are as follows: Nose and throat cultures, vaginal smear, and Wassermann were negative. Urine was free from albumin, sugar, acetone, and blood but contained free phenolphthalein during the first four days. The report on her blood was as follows: hemoglobin, 12 Gm. (72 per cent); red blood cells, 4,020,000; white blood cells, 8,500; polymorphonuclears, 51 per cent; lymphocytes, 38 per cent; eosinophiles, 9 per cent; basophiles, 1 per cent. Quantitative studies on the urine and stools of this patient while in the hospital were within normal limits. A detailed report of these studies is shown in Tables I and IA.

The child remained in the hospital under observation for seven days. She had six liquid brown stools the first day; no evacuation on the second day; one large

*We are indebted to Drs. L. Bower and I. P. Bronstein for permission to investigate and report Cases 1 and 2 and to Dr. William M. Novince (personal communication) for his report of Case 3.

TABLE I

QUANTITATIVE URINALYSIS

DATE	ALBUMIN (HEAT AND ACETIC ACID)	ALBUMIN (ROBERTS' REAGENT)	FREE PHENOLPHTHALEIN (MG. %)	CONJUGATE PHENOLPHTHALEIN (MG. %)	UROBILINOGEN (MG. %)
12/3/40	Negative	Negative	0.22	3.7	0.024 (Normal)
12/4/40	Negative	Negative	0.05	2.0	0.03 (Normal)
12/5/40	Negative	Negative	0.05	1.5	0.07 (Normal)
12/6/40	Negative	Negative	0.03	0.45	0.06 (Normal)
12/7/40	Negative	Negative	0	0.21	0.03 (Normal)
12/8/40	Negative	Negative	0	0.13	0.13 (Normal)
12/9/40	Negative	Negative	0	0.07	0.11 (Normal)

TABLE IA

QUANTITATIVE ANALYSIS OF STOOLS

DATE	WEIGHT (GM.)	MOISTURE (%)	MUCUS CHEMICAL (C.C. PER GRAM)	PROTEIN	MICROSCOPIC MUCUS		CELL STUDY	UROBILINOGEN (MG. %)
					SECRETORY	STRINGS		
12/4/40	50	81.4	0.05	0	+	0		62.4
	33	78.9	0.05	0	+	0		70.0
12/5/40	6	86.3						26.9
	16	86.0	0.04	0.01				36.1
	10	90.8	0.03	0.05				14.9
12/7/40	75	77.0	0.06	0	-	0	Normal	49.6
12/8/40	55	73.4	0.04	0	-	0	+ -	38.8
	60	70.2	0.05	0.02	-	0	Chiefly nuclei	36.6 Benzidine +

brown stool and one large green stool the third day; three soft brown stools the fourth day; no stool on the fifth; two soft, formed stools the sixth day; and no stool the seventh day. At no time were cramps or other abdominal discomfort noted. The child was always cheerful, took food normally, and showed no symptoms of dehydration or toxicity. She vomited once shortly after admission, seemingly as the result of mental excitement. Her axillary temperature varied from 97 to 98° F., and her pulse rate, from 94 to 124. No medicinal or other treatment was administered while in the hospital.

The patient was discharged in normal health on the seventh day. Neither immediate nor delayed toxic manifestations were observed.

CASE 2.—K. C. L., a 2-year-old girl, entered Cook County Hospital on Jan. 28, 1942, three hours after having swallowed six laxative tablets, each of which contained about 2½ gr. of phenolphthalein, a total of about 15 gr. The child showed no abnormal symptoms, but the parents brought her to the hospital because they thought she might need medical care. The child had no nausea, did not vomit, and had no diarrhea.

Physical examination revealed a well-developed and well-nourished, white female child who did not appear ill. The temperature was 98°; pulse, 122; respiration, 20. Heart and lung findings were normal, the abdomen was not tender or rigid, peristaltic sounds were of normal intensity, and there was no evidence of pathology elsewhere.

The laboratory examination revealed hemoglobin, 72 per cent; red blood cells, 3,940,000; white blood cells, 13,600. The Kahn test and the urine were negative.

TABLE II

QUANTITATIVE URINALYSIS

DATE	ALBUMIN (HEAT AND ACETIC ACID)	ALBUMIN (ROBERTS' REAGENT)	FREE PHENOL-PHTHALEIN (MG. %)	CONJUGATE PHENOL-PHTHALEIN (MG. %)	UROBILINOGEN (MG. %)
1/30/42	Very slight trace	Very slight trace	0.17	2.40	0.02 (Normal)
1/31/42	Very slight trace	Very slight trace	0.05	0.70	0.04 (Normal)
2/ 1/42	0	0	0.03	0.52	0.02 (Normal)
2/ 2/42	0	0	0	0.12	0.44 (Normal)
2/ 3/42	0	0	0	0.08	0.20 (Normal)
2/ 4/42	0	0	0	0.08	0.38 (Normal)
2/ 5/42	0	0	0	0.03	0.03 (Normal)

TABLE IIA

QUANTITATIVE ANALYSIS OF STOOLS

DATE	MOISTURE (%)	PHENOL-PHTHALEIN (MG. PER 100 GM.)	MUCUS CHEMICAL (C.C. PER GRAM)	PROTEIN	MICROSCOPIC MUCUS		CELL STUDY	UROBILINOGEN (MG. %)
					SECRETORY	STRINGS		
2/2/42	62.4	31.6	0.06	0.02	+	0	Changed cells +	20.00
2/5/42	74.9	0.73	0.05	0	+	0	Changed cells +	18.56 Benzidine+
2/7/42	70.1	0.25	0.05	0	+	0	Changed cells +	14.40
2/9/42	76.9	0	0.05	0	+	0	Changed cells +	32.27

Her urine and stools were collected daily and examined qualitatively and quantitatively for signs of irritation, with the results shown in Tables II and IIA.

The child was kept in the hospital for observation and study. The clinical course was uneventful. She had one large liquid and three moderately soft, greenish stools within the first twenty-four hours. There were no evacuations on the following day; a small one on the third, fourth, and fifth days. No defecation occurred on the sixth and seventh days. On the eighth day, she was given a plain water enema which produced a normal stool. On the ninth, tenth, and eleventh days no bowel movement occurred. On the twelfth day she had a normal evacuation. She was discharged from the hospital eleven days after admission.

During her stay in the hospital she behaved normally, did not show toxic symptoms such as collapse, increased or abnormal reflexes, dermatitis, or abdominal pain.

CASE 3.—A 3-year-old girl was admitted to St. John's Hospital, Cleveland, Feb. 10, 1941, at 11:20 P.M., one-half hour after she had taken sixty-five tablets of a laxative containing 2 gr. of phenolphthalein in each tablet, a total of 130 gr., according to her mother's statement. There were essentially no symptoms and no abnormal findings on physical examination.

The treatment on admission consisted of gastric lavage with sodium bicarbonate solution, three or four glasses of mustard water and pharyngeal irritation with a tongue blade to induce vomiting. This was repeated several times. Urinalysis on the following morning showed the urine to be acid, specific gravity, 1.016, no albumin or sugar, occasional pus cell in sediment. The hemoglobin was 80 per cent; red

blood cells, 4,070,000; white blood cells, 10,000. Temperature on admission was 37.4° C. (99.3° F.), the following day, 38° C. (100.4° F.), returning to normal the next day, and it remained normal until the patient was discharged from the hospital.

The treatment and clinical course while in the hospital were as follows: kaolin, 1 dr. every two hours; saline enema twice daily during the first two days; elixir phenobarbital, 1 dr. as a sedative. The child had no bowel movement the day after admission to the hospital, and a saline enema was administered without results. On the second day after admission, a saline enema was followed by a clay-colored, semi-solid stool. Later on this day, the child received castor oil (two doses of 2 dr. each), after which she had a semiliquid stool. Three days after admission, kaolin was discontinued and 2 dr. of castor oil were given.

The patient was discharged four days after admission, following an uneventful clinical course and showing no sign of any toxic influence. After discharge she continued to have normal bowel movements. Daily urinalysis showed no abnormalities during her stay in the hospital.

CASE 4.—Case 4, reported by Sachs,[10] was that of a boy 3½ years of age, who was given one chocolate laxative tablet containing phenolphthalein June 24. The following morning he ate the remaining forty-seven tablets contained in the box. The forty-eight tablets contained 96 gr. of phenolphthalein. Although the child seemed perfectly well, his mother gave him an enema which was followed by five watery evacuations within the next two hours. Shortly after this, the mother took him to the Jersey City Medical Center where he was admitted to the pediatric service. His temperature was 100° F., his pulse normal. He vomited several times after admission, and the vomitus showed a few pieces of the tablets. He had two bowel movements. There was no blood in either stool. The urine was passed in normal amounts and showed no albumin, casts, sugar, or blood. He remained in the hospital three days under observation on a bland diet and was subsequently observed in the outpatient department. Several twenty-four-hour specimens of urine were found normal, as were his blood counts.

There was no diarrhea, no skin eruption, nor any other untoward symptoms. No medication was given the child while in the hospital. Sachs concluded that "the absence of ill effects in my case after an overdose of 96 gr., as well as the numerous other instances in which large overdoses had caused no ill results, lends support to the view of Vamossy and others who are convinced that phenolphthalein does not produce harmful disturbances in man."

DISCUSSION

The results of daily urine examination in the child in Case 1 for one week following the ingestion of 12 gr. of phenolphthalein were essentially negative. The total absence of albumin in the urine during this period would indicate that 12 gr. of phenolphthalein ingested as a single dose did not produce a kidney irritation, although both conjugate and free phenolphthalein were found. Traces of free phenolphthalein were present in the urine on the first four days. This is usual in fresh urine when the conjugated phenolphthalein reaches a concentration of approximately 3 mg. per 100 c.c. and is commonly found if the urine is examined after standing for a number of hours at room temperature. Both factors were present, since there was a concentration of greater than 3 mg. per 100 c.c. on the first day, and in addition, the specimens were twenty-four hours old when examined. The amount of conjugate phenolphthalein in the urine is an index of the quantity absorbed from

the intestinal tract. In this case it did not exceed the amount often found after the ingestion of a prescribed laxative dose. The amount of urobilinogen remained within normal limits and is considered evidence that this phase of liver function was not impaired.

The results of four stool analyses in Case 1 revealed that the original weight of the stool was not excessive, and the amount of moisture fell within normal limits. Approximately 0.1 c.c. of mucus per gram of stool occurs normally. Greater amounts are considered evidence of hypersecretion. In this case the amounts were well below this maximum figure. This was confirmed by microscopic examination of the stool which showed the presence of the so-called "secretory" mucus but no mucous strings which are found when irritation of the intestinal mucosa occurs. Transient traces of protein (0.01, 0.02, and 0.05 per gram) were found in the stool. These findings are without significance, since on four other occasions no protein was found, and only the constant occurrence of protein in large amounts is considered evidence of irritation. A weekly positive benzidine reaction, as found on one occasion, is not an uncommon finding, especially in children who have not been on a meat-free diet. A cell study of these stools showed a normal cytology; in some instances no leucocytes, and in others, degenerated cells only. The absence of normal-appearing leucocytes in the feces is evidence that there was neither inflammation nor irritation of the bowel. The urobilinogen in the various stool samples ranged from 14 to 70 mg. per cent (normal, 30 to 200 mg. per cent).

Daily urinalysis in the child in Case 2 showed an absence of albumin during five successive days, following a very slight trace on the first two days. In this case, as in Case 1, free phenolphthalein was found in small amounts in the first three twenty-four-hour specimens of urine. Conjugate phenolphthalein of 2.40 mg. on the first day may have been a factor in the production of free phenolphthalein in the specimen. The other factor is that the urine, with fairly high conjugate values, was left standing at room temperature, and this allowed the release of a measurable amount of free phenolphthalein. In this case, as also in Case 1, normal values for urobilinogen were present, laboratory evidence that liver function was normal and uninfluenced by large doses of phenolphthalein.

Stool moisture was within normal limits. Phenolphthalein was eliminated unchanged in large amounts on the first day and in sharply decreasing amounts on succeeding days. By the end of the week it had disappeared entirely from the stool. Chemical mucus in this instance was within normal limits. The first stool examined showed a 0.02 c.c. content of protein per gram of stool. It is not possible to state whether this was due to irritation, for in this instance, as in Case 1, the child had a positive benzidine test. The fact that the protein appeared only on the first day of observation and did not recur on three successive

examinations would seem to indicate an undamaged intestinal tract. The findings of "secretory" mucus microscopically was within normal limits. The cytology of the stool showed only the usual "changed cells" indicative of the absence of acute intestinal irritation. Urobilinogen was present in all stools examined. The amounts, 14 to 32 mg. per cent, are lower than usually considered average, but this is not considered of pathologic significance.

CONCLUSIONS

1. No significant pathology is produced from the ingestion of doses of phenolphthalein many times greater than that recommended by the United States Pharmacopoeia and National Formulary as a laxative for children.

2. The lethal dose has not been determined for experimental animals. Death could not be produced in the animals tested by the administration of phenolphthalein.

3. There is no indication for the use of "heroic" measures such as gastric lavage, since an "overdose" of phenolphthalein has no effect on the child.

4. There is no clinical indication for the use of activated charcoal followed by castor oil after the ingestion of an "overdose" of phenolphthalein, since the drug is eliminated promptly with very little discomfort and no measurable toxic effect.

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CIRCULATION TIME IN INFANTS AND YOUNG CHILDREN DETERMINED BY THE FLUORESCEIN METHOD

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CIRCULATION time in man has been ascertained by several methods, but there have been few determinations (Table I) in infants and children because most of the methods have had serious objections to their use in these age groups. The intravenous injection of saccharin[5] or decholin[2] requires that the subject signal the instant he experiences the sweet or bitter taste, respectively. These are subjective tests which are unreliable in infants and young children. The histamine injection test[3, 4] depends upon noting the time at which flushing of the face occurs and the cyanide method,[7] on noting the instant that respirations are increased by the action of the drug on the carotid sinus. Although both are objective tests, most children cry when their vein is pierced by a needle and crying interferes with the signal reaction upon which the accuracy of the circulation time primarily depends. The radium emanation methods[1, 6] are accurate objective tests but are complex procedures which may produce toxic reactions and cannot be repeated after a short interval of time.

Robb and Weiss[7] have stated that a chemical substance suitable for measurement of the velocity of blood in man should fulfill the following requirements: (1) should be nontoxic in the dose used; (2) should not influence the velocity of the blood flow until the signal reaction has occurred; (3) should be repeatable after a short period of time; (4) the signal reaction should be objective; (5) the signal reaction should occur promptly after the arrival of the active agent in the reaction organ; and (6) the signal reaction should be readily discernible in both normal and abnormal conditions.

The fluorescein test for circulation time which has been developed by Lange and Boyd[8, 9] is a relatively simple procedure that meets all these requirements and readily lends itself to use in all age groups. It makes use of the properties of the dye, fluorescein, which is injected intravenously without producing toxic effect and which gives off an intense green fluorescence when exposed to ultraviolet light. The fluorescein is prepared as a 5 per cent solution in five per cent sodium bicarbonate. The source of the ultraviolet light employed is a simple, inexpensive, mercury vapor lamp* provided with a glass filter which absorbs most of the visible rays and throws a faint purple light with a wave length of from 3,600 to 4,000 Angström units.

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*Manufactured by Continental Lithographing Co., New York, N. Y.

TABLE I

AUTHOR	METHOD	NUMBER OF CASES	AGE GROUP	CIRCULATION TIME (SEC.)
Blumgart and Weiss[1]	Active radon	22	12 to 15 yr.	12 to 23
Tarr, Oppenheimer, and Sager[2]	Sodium Dehydrocholate	8	10 to 14 yr.	10 to 13
Seckel[3]	Histamine	30	6 to 15 yr.	17 to 30
Seckel[4]	Histamine	50	Up to 2 yr.	14 to 17
Averbuck and Friedman[5]	Saccharin	100	8 to 16 yr.	5 to 13.5
Hubbard, Preston, and Ross[6]	Radioactive Sodium	22 14	3 to 14 yr. 1½ to 22 mo.	5 to 17 (Average, 11) 3 to 12 (Average, 7)
Witzberger and Cohen	Fluorescein	51 25	3 to 13 yr. 1 to 24 mo.	7 to 16 (Average, 11.5) 5 to 9.1 (Average, 7)

TECHNIQUE OF TEST

The subject is permitted to rest quietly for about one-half an hour before the test is performed. The calculated dose of fluorescein (0.07 c.c. per kilogram of body weight) is drawn up into a 1 or 2 c.c. syringe, and a suitable arm or hand vein is entered. The lights are then turned off and the glow from the ultraviolet lamp is directed into the subject's face. A few minutes are permitted to elapse after insertion of the needle so that the initial apprehension of the patient subsides. The dye is then injected rapidly. The operator's assistant starts a stop-watch at the same instant that the injection is begun and stops the watch the instant that he first notices the green fluorescence in the subject's lips. The lips of colored children appear slightly greenish yellow in the ultraviolet light before any dye is injected, but, if the operator takes this into account, there should be no confusion in recognizing the instant that the true fluorescence makes its appearance. The signal reaction is easily discernible, and if several observers time the interval between the injection and the first appearance of the fluorescence, they will rarely disagree by more than one second.

RESULTS IN CHILDREN THREE TO THIRTEEN YEARS OF AGE

The arm-to-lip circulation time was determined in fifty-one young children, 3 to 13 years of age, who had a variety of diagnoses but no demonstrable cardiovascular disturbances. The fluorescein solution employed for the first few children was prepared in our laboratory and caused vomiting in two instances. For all the other subjects we used a commercially prepared solution* of the dye and none of these children had any noticeable reaction.

The tabulated results (Table II) are arranged according to age, and there seems to be a tendency for the younger children to have a shorter

*Marketed in ampoules by C. F. Kirk Co., New York, N. Y.

TABLE II

CIRCULATION TIME OF FIFTY-ONE CHILDREN THREE TO THIRTEEN YEARS OF AGE

DIAGNOSIS	AGE (YR.)	WEIGHT (POUNDS)	PULSE	CIRCULATION TIME
Gonococcal vaginitis	3	28	90	7.3
Preoperative T. and A.*	3	32	100	9.0
Cervical adenitis	3	31	96	8.0
Pneumonia (convalescent)	3	34	100	10.2
Pyodermia	4	38	80	10.3
Preoperative T. and A.	4	42	88	10.0
Rhinopharyngitis	4	35	85	12.0
Cervical adenitis	4	39	90	10.0
Preoperative T. and A.	5	52	100	12.0
Preoperative T. and A.	5	46	100	9.0
Preoperative T. and A.	5	51	84	13.2
Acute nephritis (convalescent)	5	51	108	11.8
Cervical adenitis	6	62	92	14.4
Cervical adenitis	6	32	100	7.0
Tinea capitis	6	55	90	11.0
Vincent's stomatitis	6	37	100	11.2
Cervical adenitis	6	50	86	13.4
Preoperative T. and A.	6	52	88	13.0
Malnutrition	6	30	90	10.0
Fracture of mandible	7	57	88	15.0
Preoperative T. and A.	7	42	100	9.4
Preoperative T. and A.	7	58	96	10.0†
Preoperative T. and A.	7	47	86	11.0†
Preoperative T. and A.	7	47	108	10.6
Hilar tuberculosis	8	63	80	13.2
Idiopathic convulsions	8	62	84	14.0
Pneumonia (convalescent)	8	57	100	10.0
Rhinopharyngitis	8	60	90	12.0
Vincent's stomatitis	9	55	110	11.2
Gonococcal urethritis	9	58	84	14.0
Catarrhal otitis media	9	60	80	13.0
Abdominal hernia	9	56	100	14.2
Tinea capitis	9	53	90	15.0
Bronchitis	10	67	82	12.0
Fractured femur	10	65	86	13.0
Cervical adenitis	10	66	80	12.4
Fractured femur	11	58	86	8.3
Cervical adenitis	11	84	80	13.6
Cervical adenitis	11	84	80	16.0
Preoperative T. and A.	11	79	88	16.0
Preoperative T. and A.	11	59	90	10.0
Preoperative T. and A.	11	105	78	8.0
Mental defective	11	72	96	13.6
Pneumonia (convalescent)	12	80	90	11.6
Primary complex tuberculosis	12	86	100	13.0
Bronchitis	12	72	80	11.0
Hemiplegia	12	60	96	13.2
Bronchitis	13	94	80	13.2
Upper respiratory infection	13	98	78	11.0
Preoperative T. and A.	13	98	84	12.0
Pneumonia (convalescent)	13	104	80	13.0

*Tonsil and adenoid cases.

†These two children vomited following the injection of a fluorescein solution prepared in our laboratory.

circulation time. However, two of the 11-year-old children have a rate of only 8 seconds, and one of the 4-year-old children has a rate of 12 seconds. There is no exact correlation between the pulse rate and the circulation time in this group of children, for a 7-year-old child with a

pulse of 100 has a rate of 15 seconds, while the 11-year-old with a rate of 8 seconds has a pulse of 78.

The arm-to-lip circulation time in this group of fifty-one children, 3 to 13 years of age, averaged 11.5 seconds, with a range of from 8 to 16 seconds. These results compare very closely with those of Hubbard and associates,[6] who studied a comparable group of children with an accurate radium emanation method. They reported an average rate of 11 seconds, with a range of from 5 to 17 seconds.

RESULTS IN INFANTS ONE TO TWENTY-FOUR MONTHS OF AGE

The arm (or hand)-to-lip circulation time was determined in twenty-five infants, 1 to 24 months of age, who had a variety of diagnoses but no demonstrable cardiovascular disturbances. An antecubital vein was used in most cases, but in a few instances a small vein on the back of the hand was utilized. This slight increase in the length of the route traversed by the dye did not noticeably increase the time interval. The signal reaction in the fluorescein test is not affected by crying.

The rates in this group of twenty-five infants, 1 to 24 months of age (Table III), averaged 7.0 seconds, with a range of from 5.0 to 9.1 seconds. These results are also in agreement with those of Hubbard and associates,[6] who reported an average rate of 7.0 seconds with a range of from 3 to 12 seconds.

TABLE III

CIRCULATION TIME OF TWENTY-FIVE INFANTS ONE TO TWENTY-FOUR MONTHS OF AGE

DIAGNOSIS	AGE	WEIGHT (POUNDS)	PULSE	CIRCULATION TIME (SEC.)
Contact dermatitis	4 wk.	11	130	5.0
Upper respiratory infection	4 wk.	8	150	6.0
Upper respiratory infection	6 wk.	9	150	7.0
Congenital laryngeal stridor	6 wk.	7	136	8.0
Infantile eczema	7 wk.	12	150	8.2
Upper respiratory infection	8 wk.	10	140	7.0
Normal infant	3 mo.	16	140	6.4
Upper respiratory infection	3 mo.	14	140	6.5
Rectal prolapse	3 mo.	12	138	6.2
Upper respiratory infection	4 mo.	14	134	6.8
Upper respiratory infection	5 mo.	14	128	5.4
Upper respiratory infection	5 mo.	15	126	6.0
Parenteral diarrhea, convalescent	6 mo.	15	120	5.2
Infantile eczema	6 mo.	17	130	5.0
Upper respiratory infection	7 mo.	16	124	7.6
Infantile eczema	8 mo.	15	142	8.2
Infantile eczema	9 mo.	22	120	7.8
Pneumonia (convalescent)	12 mo.	22	120	7.5
Pneumonia (convalescent)	15 mo.	26	116	6.5
Pneumonia (convalescent)	16 mo.	23	112	8.2
Nutritional anemia	18 mo.	20	110	8.0
Infantile eczema	18 mo.	25	90	6.5
Infantile eczema	21 mo.	28	130	7.5
Aphthous stomatitis	24 mo.	32	108	9.1
Preoperative T. and A.	24 mo.	27	100	9.0

SUMMARY AND CONCLUSIONS

1. Circulation time in infants and young children was measured by determining the time between the injection of fluorescein into an arm vein and the appearance of fluorescence in the subject's lips.

2. The fluorescein test is a suitable objective method for determining the circulation time in infants and young children. The simplicity and directness of this method would seem to indicate a wide application.

3. Circulation time in fifty-one children between 3 and 13 years of age averaged 11.5 seconds, with a range of 7.0 to 16.0 seconds.

4. Circulation time in twenty-five infants between 1 and 24 months of age averaged 7.0 seconds, with a range of 5.0 to 9.1 seconds.

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PREMEASLES ENCEPHALITIS

Report of a Case

Harry H. Clemens, M.D.
Marysville, Calif.

BY PREMEASLES encephalitis, we are referring to neurologic manifestations arising before or during the invasive stage of measles, before the appearance of the Koplik spots, the enanthem or the exanthem, in contradistinction to postmeasles encephalitis, where the nervous system complications appear following the prodromes. The incidence of encephalitis occurring before the precursory signs of measles is considerably below that found in the postmeasles encephalitis (0.1 to 0.2 per cent).[1] Thus far only seventeen such cases of encephalitis have been recorded in the literature.

Herein is reported an additional case of encephalitis preceding measles. Because of the confusion in arriving at an early diagnosis and its similarity in signs and symptoms to other cerebral pathology, we feel justified in describing this unusual case.

REPORT OF A CASE

J. H. H. (Case No. A-54756), a white boy aged 6 years, was admitted to the pediatric service of the Grady Hospital, Atlanta, Ga., March 20, 1941, with the statement by his mother that he complained of seeing two of everything. The birth and development of the patient were normal. His past health had always been good except for uncomplicated mumps at the age of 2 years and uncomplicated chicken pox at the age of 3 years. He had always appeared to be an intelligent and alert child. The father and mother were in good health. There was no familial history of tuberculosis, syphilis, or any neurologic disturbances. There were five other siblings, all in good health at the time of the patient's admission, but they subsequently developed measles without complications during his stay in the hospital.

The onset of this illness began on March 15, 1941, five days before admission, when the patient stated that he saw "two mummies and two daddies." No attention was paid to this complaint because of its short duration, lasting only over a period of several hours. He had no fever and did not appear ill at that time. On the day before admission, March 19, 1941, the patient again complained of double vision. Later in the day he staggered about in his walk and on arrival at the hospital was unable to stand or sit without falling to the right.

There was no history of vomiting, upper respiratory infection, diarrhea, ear disease, or head injury preceding the illness. The mother observed that the child had a little fever, for the first time in the illness, the day before admission.

The patient was a well-developed and well-nourished male, 6 years of age, lying quietly with the upper limbs flexed and the lower ones extended. The temperature was 100° F.; pulse, 90; respiration, 20; and blood pressure, 100 mm. systolic and 60 diastolic.

From the Department of Pediatrics, Grady Hospital, and Emory University, School of Medicine, Atlanta, Ga.

The skin was free of any lesions. The mouth was clean without odor, and no lesions were present. The color of the hair was red. The conjunctivas were clear and uninflamed. Slow vertical movements of the eyeballs were present; the quicker movements which appeared to be superior at first, on later examinations were seen to be inferior. The ophthalmoscopic examination revealed a paleness of the nasal half of the right disc. The fundi appeared normal. The nasal passages were clear and free of any discharge or inflammation. Nuchal rigidity was present to a moderate degree. No lymphadenopathy was present. The abdomen was scaphoid; no masses were palpable, and there was no enlargement of the spleen or liver. The heart and lungs were essentially negative. The extremities were in a state of flaccidity, but the tone of the muscles was good. All the deep

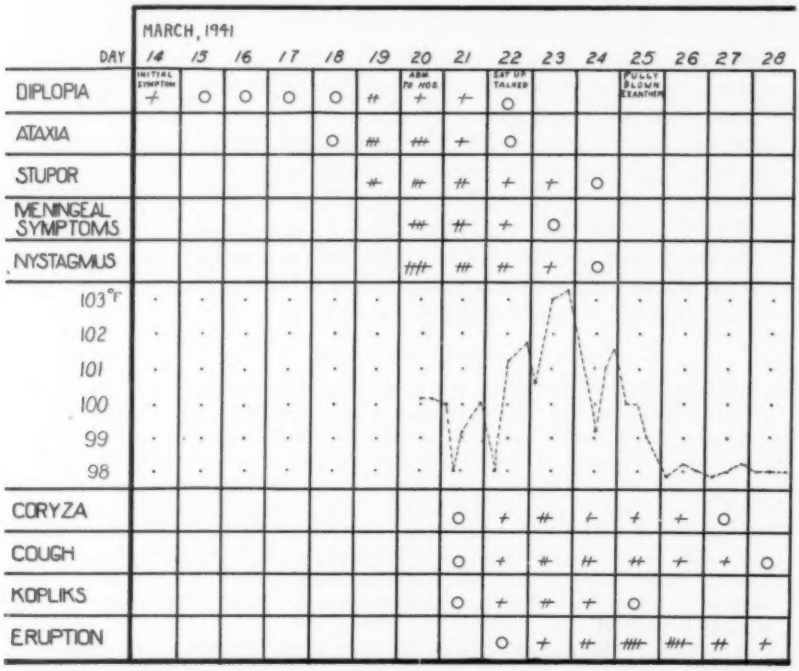

Fig. 1.—Encephalitic signs and symptoms preceding the prodromes of measles and ceasing as the eruption began to develop. The initial symptom of diplopia occurred eleven days before the fully blown rash.

reflexes were present, those on the right side being definitely hyperactive. The superficial reflexes were present and active. Babinski's sign was negative. Both Kernig and Brudzinski's signs were positive to a marked degree.

It was felt by the house staff that the signs and symptoms pointed toward: (1) labyrinthitis, (?) etiology, (2) cerebellar irritation or tumor, and (3) tuberculous meningitis. There was no suggestion of measles.

Several examinations during the course of the next twenty-four hours revealed a great variability of the signs. For the most part, the child lay in a semicoma, making no movements, being apathetic, not responding to questions and staring into space. Rarely there were spontaneous purposeless movements of both upper and lower extremities, apparently equal on both sides. He was at times able to

distinguish coins and followed movements well. When he attempted to walk, after being aroused and stood on his feet, he deviated markedly and stumbled constantly to the right.

Laboratory Data.—The urine on the day of admission was negative and remained so throughout his hospital stay. The red blood count was 4,300,000; the hemoglobin (Sahli) was 12.6 Gm. (80 per cent) per cubic millimeter. The white cell count was 10,000 per cubic millimeter, with 64 per cent polymorphonuclears, 34 per cent lymphocytes, and 2 per cent monocytes. The blood sugar was 106 mg. per 100 c.c. of blood; the nonprotein nitrogen was 20 mg. per 100 c.c. of blood. The blood Kahn was negative. The purified protein derivative test, second strength, was negative.

After consultations with the neurologist, a cautious spinal puncture was performed. The fluid was clear and under slightly increased pressure. There was one lymphocyte per cubic millimeter, and no increase of globulin was noted. The Levinson test was negative. The Kahn test of the spinal fluid was negative. Culture of the spinal fluid revealed no growth after ten days.

A neurologic examination March 24, 1941, by Dr. Wilson, medical neurologist, pointed toward an encephalomyelitic process or possibly an angioneurosis of the brain. Examination by an otologist leaned toward the impression of a cerebellar lesion. Tests of the labyrinth were not satisfactory.

Course.—All therapy was symptomatic. Fig. 1 reveals the subsequent course. As the neurologic signs subsided, the signs and symptoms of measles appeared, or vice versa. Daily physical examinations were performed. In the first few days, several examinations were performed daily. The first Koplik spots were seen three days after admission. On the third hospital day, the patient sat up and talked. The typical measles exanthem was present six days after admission. Dr. Hackney, epidemiologist, the city of Atlanta, Ga., confirmed the diagnosis of measles on March 25, 1941. Nine days after admission the patient was discharged, improved, to the care of his parents. The neurologic examination at that time was normal in all respects. The patient was alert, and according to the parents, appeared his normal self. Re-examination two months later revealed no residua or abnormalities.

COMMENT

Nervous symptoms in measles may appear apparently at any time in the course of the disease, but usually occur following the onset of the exanthem (second to the third day,[2] third to the sixth day,[3] fourth to the sixth day,[4] fifth to the eighth day,[5] fifth to the fifteenth day,[6] etc.). Cases of measles encephalitis as early as six days preceding the rash and as late as forty-two days following the rash have been described.[7] The age incidence for postmeasles encephalitis is usually given as between one and fourteen years. Five cases have been reported in infants under 1 year of age.

Strong[8] states that prior to ten years ago, measles involvement of the central nervous system was definitely infrequent.

One case of encephalitis per 1,000 cases of measles is accepted as the usual number occurring in an epidemic.[1] In the experience of some, the figure should be higher.[2] Most of the reports have appeared in the literature since 1925. There has been a marked increase in the past few years.[5, 8]

Polymorphism of signs from the very mild to the severe is the rule. Measles involvement of the nervous system is quite variable, and, as

recognized today, includes syndromes involving the cerebrum, cerebellum, spinal cord, and the cranial nerves. The lesions may be focal or diffuse, single or multiple. The differentiation of the acute toxic encephalitis from the true encephalomyelitis of the white matter is stressed by Putnam.[9]

Cerebral complications of measles were either rare or else overlooked by the older writers on the contagious diseases. Corlett[10] listed the following involvement by measles of the nervous system: (1) disseminated myelitis; (2) hemiplegia; (3) false disseminated sclerosis; (4) muscular atrophy; (5) chorea; (6) mental disorder (apathetic condition, "mania").

In 1928 Ford[7] collected 113 reports of measles encephalitis and added twelve of his own. Four cases in the collection are of the premeasles encephalitis type. The case of Rilliet and Barthez is mentioned. Their patient, a female infant 1 year of age, six days before the measles rash had "violent convulsions on the left and then on the right. The next day the patient had a right hemiplegia accompanied by fever. Recovery occurred in five days." Recovery evidently occurred at the height of the measles eruption and in this respect is similar to our case. Boenheim[5, 7] reported on 5,940 cases of measles, twenty-three patients of whom had nervous symptoms, but only six were of the nature of encephalitis. More recently (1941) Hamilton and Hanna[2] reported on 285 cases of measles encephalitis, forty-four of which were their own. In one of their cases, the complication of encephalitis preceded the rash by five days.

SUMMARY

1. A case of measles encephalitis preceding the Koplik spots is reported. The initial symptom occurred eleven days before the height of the exanthem.

2. The course of the encephalitis resembled cerebellar or labyrinthine involvement.

3. Recovery was rapid and spontaneous as soon as the exanthem appeared.

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Correspondence

DR. BORDEN S. VEEDER, EDITOR:

I wish to correct an apparent misquotation appearing in the paper by Dr. Joseph H. Lapin on "Mixed Immunization in Infancy and Childhood," which you published in April of this year.

In referring to a paper by Miss T. M. Saito and myself entitled, "Concurrent Immunization Against Tetanus, Diphtheria, and Pertussis," The Journal of Pediatrics, vol. 21, page 31, July, 1942, Dr. Lapin writes (vol. 22, page 447):

> At this point note should be made of the viewpoint of Miller and Saito, that, if high levels of tetanus antitoxin are secured, the boosting dose of toxoid on exposure (to tetanus) may be dispensed with.

On the contrary we do not hold this view and have not recommended "dispensing with a booster injection." In our paper we showed that an actively induced level of tetanus antitoxin between 0.1 and 1.0 units per c.c., which is as high as can be attained by the usual prophylactic dose of 1,500 units of antitoxin, can be maintained for a year when certain agents and time intervals are used. In the experience of Bigler and Werner and ourselves, three injections of combined alum-precipitated diphtheria and tetanus toxoids (or two injections of the combined toxoids and a third of alum-precipitated tetanus toxoid), when given at three-month intervals, result in such levels. We therefore recommended these procedures, together with annual re-injections, for the following reason.

The child's wound or scratch may not be called to the attention of the physician by the parent. The very fact that the child has had "shots" predisposes to parental complacency. The trauma may be inflicted under circumstances where neither a physician nor toxoid is available. This is often the case in rural or mountainous areas today. Under such circumstances the amount of circulating tetanus antitoxin the child has at the time he is infected may be of the greatest importance.

Toxin liberated by bacilli growing in wounds has been shown to be a relatively poor antigen. A child having over 0.1 unit per c.c. of homologous, "home grown" antitoxin at the time of trauma will be as well off as if he had received 1,500 units of prophylactic antitoxin. Another child "basically immunized" but with only 0.01 unit of antitoxin per c.c. might succumb to tetanus. Boyd and Maclennan have recently reported three deaths in actively immunized soldiers. They had received fluid tetanus toxoid in the past and no booster injection at the time of trauma. Even in the armed forces "boosters" cannot always be given.

We concluded our paper by saying that "although this [the above recommended] dosage may be more than necessary to secure basic immunity, it is desirable in that it results in the maintenance of high levels of antitoxin for a year. Such high levels would be important instances in which toxoid reinjection at the time of injury was neglected or impossible."

May I request that you publish this explanatory note.

(Signed) JOHN J. MILLER, JR., M.D.

SAN FRANCISCO
APRIL 29, 1943

The Pediatrician and the War

Emergency Appropriation for Maternity and Child Care

The following excerpts are taken from MCH Information Circular No. 13, issued in March, 1943, by the Children's Bureau:

> The First Deficiency Appropriation Act of 1943, was approved March 18, 1943, making available an appropriation of $1,200,000 for the period ending June 30, 1943, "for grants to States, including Alaska, Hawaii, Puerto Rico, and the District of Columbia, to provide, in addition to similar services otherwise available, medical, nursing, and hospital maternity and infant care for wives and infants of enlisted men in the armed forces of the United States of the fourth, fifth, sixth or seventh grades, under allotments by the Secretary of Labor and plans developed and administered by State health agencies and approved by the Chief of the Children's Bureau."
>
> This excludes the families of commissioned officers; of master, major, first, technical, staff, and platoon sergeants; and of chief, first, and second-class petty officers.

Eligibility for Care Under the Plan

> Any woman in the State, irrespective of legal residence, whose husband is an enlisted man (this includes men deceased or missing in action) in the armed forces of the United States of the fourth, fifth, sixth, or seventh grades (Army, Navy, Marine Corps, or Coast Guard), and who makes application for such care, will be eligible for the medical and hospital maternity services provided under the plan, without cost to the family, when similar services are not otherwise available from the medical or hospital facilities of the Army or Navy or from facilities provided by or through official State or local health agencies.
>
> Similarly, any infant under 1 year of age, whose father is an enlisted man as described in the previous paragraph, will be eligible for pediatric and other medical, surgical, and hospital care provided under the plan.

Maternity Care

> Payments to private physicians participating in the program should be made on a case basis rather than a fee-for-visit basis.

Health Supervision and Medical Care for Infants

> Medical care for sick infants requiring three visits or more by a private physician should be financed on a case basis, such as $10 for home and hospital medical care during the first week of illness and $5 for home, office, and hospital medical care for succeeding weeks, with a minimum of three visits per week and for periods not longer than three weeks. Recommendations concerning the basis on which compensation will be paid for care for minor illnesses requiring less

than three visits will be issued later. Renewal of authorization for more prolonged medical care of infants should be given only after review of the case by the maternal and child health director or a pediatric consultant appointed by the State health agency. Rates of payment for medical services rendered by pediatricians who are certified by the American Board of Pediatrics or assistant consultants who have had one or more years of graduate training in pediatrics in an approved residency may be approximately one-fourth to one-third higher than the rates of payment for services rendered by physicians who have not had such additional graduate training and experience.

Payments should be made to the attending physicians or consultants by the State health agency on the basis of invoices, accompanied by completed medical records, on forms prepared by the State health agency for this purpose after approval by the State maternal and child health director or his deputy. Copies of these forms should be submitted as a part of the plan.

Standards: Medical Services

Medical care provided under the plan may be authorized only when the attending physician or consultant is a graduate of a medical school approved (at time of graduation or subsequent to graduation) by the Council on Medical Education and Hospitals of the American Medical Association. For the period of this emergency program, individual exceptions may be made when a person with a degree of Doctor of Medicine who is not a graduate of a medical school approved (at time of graduation or subsequent to graduation) by the Council on Medical Education and Hospitals of the American Medical Association has completed postgraduate training in obstetrics and/or pediatrics which, in the opinion of the State health officer and his technical advisory committee, makes him competent to participate in the program.

The following is a continuation list of Fellows of the American Academy of Pediatrics on active duty in the military services:

Army

Dr. James W. Britton, Anniston, Ala. (Captain)
Dr. Charles B. Etter, Memphis, Tenn. (Major)
Dr. C. Jack Harrison, Chicago, Ill. (Major)
Dr. Bruce A. Knickerbocker, Dallas, Texas (Major)
Dr. Thomas M. Lamb, Brooklyn, N. Y. (Major)
Dr. Oscar B. Markey, Cleveland, Ohio (Major)
Dr. Aims C. McGuinness, Philadelphia, Pa. (Major)
Dr. Philip S. Potter, Berkeley, Calif. (Colonel)
Dr. Samuel X. Radbill, Philadelphia, Pa. (Captain)
Dr. Carl L. Ruder, Pittsburgh, Pa. (Major)
Dr. Walter B. Seelye, Seattle, Wash. (Captain)
Dr. Hyman A. Slesinger, Windber, Pa. (Major)
Dr. Lendon Snedeker, Boston, Mass. (Major)
Dr. Roland Stahr, Reno, Nev. (Captain)
Dr. Hugh C. Thompson, Jr., Tucson, Ariz.

Dr. Norman T. Welford, LaGrange, Ill. (Captain)
Dr. A. Alvin Wolf, Chicago, Ill. (First Lieutenant)
Dr. Byron P. York, Houston, Texas (Major)

Navy

Dr. Raymond F. Grissom, Oak Park, Ill. (Lieutenant Commander)
Dr. Harry H. Horwitz, Oakland, Calif. (Lieutenant Commander)
Dr. Harold Jacobziner, New York, N. Y. (Lieutenant Commander)
Dr. Marion G. Josephi, New York, N. Y. (Lieutenant)
Dr. Thomas F. Reilly, Springfield, Mass. (Lieutenant Commander)
Dr. D. William Scotti, New York, N. Y. (Lieutenant Commander)
Dr. Walter M. Whitaker, Quincy, Ill. (Lieutenant Commander)

Special

Dr. Bernard Zuger, Brooklyn, N. Y. (Surgeon, U. S. Public Health Service)

American Academy of Pediatrics

Proceedings

TWELFTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CHICAGO, ILL., NOV. 4-7, 1942

Panel Discussion on Growth and Development

Chairman: Joseph A. Johnston, M.D., Detroit, Mich.

Associates: John E. Anderson, Ph.D., Director, Institute for Child Welfare, University of Minnesota, Minneapolis, Minnesota.
Julian D. Boyd, M.D., Iowa City, Iowa.
Norman C. Wetzel, M.D., Cleveland, Ohio.

Growth and Development From the Clinician's Standpoint

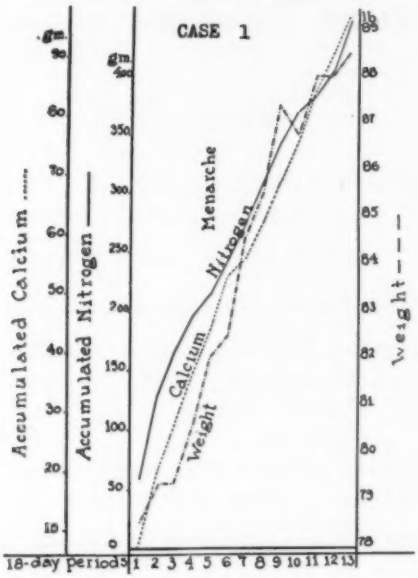
Joseph A. Johnston, Detroit

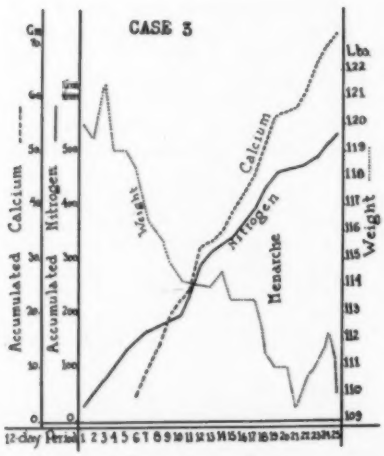
From the numerous excellent cross-section and longitudinal studies of growth and development in progress throughout this country and from very many contributions to an understanding of the various factors which influence growth, it is the hope of this panel from time to time to offer the clinician a critical evaluation of at least some of the factors which have clinical importance and, in addition, to bring back to the student of growth and development unsolved problems which confront the practicing physician daily in his office. On few controversial points will it be possible to make any dogmatic pronouncements; in many instances we can offer only a personal opinion. If we can bring into bolder relief our ignorance, we shall have accomplished much. I suppose that one of the chief contributions of the 1930 White House Conference was just that, and largely as a result of it tremendous stimulus was given to the farsighted programs in such places as Colorado, Harvard, Columbia, and many other universities.

We need not apologize for taking the time for a panel such as this at a time like this if we can justify it by any contribution to the optimal growth and development of the generation that must carry on the burden that the present catastrophe will leave behind.

That growth is not just a straight line but is made up of a series of curves, depicting changing rates, does seem to have more than academic importance. Robertson suggested that there were three critical points in the growth curve of a child, dependent on the speed of growth: one at the end of the first year, one at the end of the preschool age, and one around puberty. You can think of many of these things in your own practice; the bony changes of rickets have their peak incidence at the

first point, the osteochondroses at the second, and at puberty the slipped epiphyses appear coincidentally with an altered speed of growth which precedes sexual maturity. At these three points there would seem to be a depressed ability to retain basic substrates which corresponds to what one might expect as a growth curve goes from an accelerated to a decelerated phase. Whether this is the positive effect of a hormone, in the case of the puberty curve of the sex hormone, or is inherent in the





Charts illustrating variations in the composition of growth. In Case 1 nitrogen and calcium are accumulated parallel with increase in weight. In Case 3 weight is being lost while calcium and nitrogen are being gained. (Reprinted from Am. J. Dis. Child. 59: 287, 1940.)

curve of the chemical processes involved in growth is not clear. It has clinical importance, however, in warning us that during these times particular effort should be made to satisfy requirements for those items which enter into structure.

There is a limit beyond which growth cannot be stimulated. When there are considered those elements that enter into growth—nitrogen in muscle, calcium in bone—an increase in intake does not always result in an increase in retention. If there has been a deficit to be corrected, tremendously high retentions occur until the deficiency has been made up, but normally larger intakes produce larger retentions only to a certain level determined probably by inheritance.

A few of these physiologic principles can best be illustrated by a number of slides. The first of these, taken from a study of the protein requirement of children, demonstrates that an increase in the intake of protein is paralleled by an increase in the retention of nitrogen only up to a certain point beyond which the excess is rejected. With calories adequate, this corresponds to a protein intake of approximately 18 or 20 per cent of the total calories. An exception occurs in the case of a child who has previously been underfed; here there is an avid retention of nitrogen until previously depleted stores have been filled.

A similar finding is illustrated in the case of calcium. No retention at all occurs until a critical point is reached, following which retention increases parallel with intake until the so-called physiologic ceiling is reached, which, in the case of the adolescent girl studied, proved to be 2.0 Gm. without added vitamin D. An increased efficiency of utilization occurs with the addition of this vitamin. The point to be made, however, is that in the case of this "basic substrate" there is a fixed limit to the amount which can be added to the body as a result of increased intake.

Under usual circumstances increase in total mass and the development of bone and muscle proceed roughly parallel with each other, but there are numerous exceptions to this which have clinical importance.

The third slide brings out the fact that it is possible to reduce the obese child's weight while permitting him to accumulate nitrogen and calcium at the usual rate. With total calories reduced for this purpose, it was merely necessary to increase relatively the amounts of nitrogen and calcium in the diet. The converse of this situation appears in the fourth slide in which there is illustrated a steady loss of nitrogen with a deceptively reassuring gain in weight in a child with tuberculosis. We have come to associate such a finding with a spread of the disease and to question the practice of rapidly promoting weight gain in this group unless it is accompanied by adequate retentions of nitrogen and calcium.

These studies are presented to stress two points: (1) that there is a limiting factor which prevents the addition to the body of basic structural substances and (2) that it is at least as important to consider the composition of growth as it is to assess the total mass accumulation recorded in terms of weight, height, or other over-all measurement. In a practical clinical way, this is possible only by inference from a knowledge of required intake and of the factors influencing its utilization.

The fact remains that we need some means of appraising the average child, and to my mind the practical application of that has been made by Dr. Wetzel.

Appraisal of Growth and Development

Norman C. Wetzel, Cleveland

Matters of growth and development have always been vitally important except perhaps to the ox-eyed goddess, Athena, who sprang full grown from Zeus' brain. Under her aegis, however, these matters today become grave and serious, for who can deny that the strength of the next and succeeding generations, as well as the

outcome of the present-day children, does not depend in the very first place upon growth and development? The responsibility of the pediatrician in taking the lead to promote the best but not necessarily the maximum response of which each child is capable stands before us more clearly than ever, for it is the clinical side of the problem that is ultimately involved when growth and development have failed. Since every child faces the risk of failing in growth, it is obviously also a responsibility of the pediatrician to decide whether growth and development are proceeding satisfactorily or whether a child is on the way toward failure.

But the task of continued surveillance may easily become unmanageable unless the problem of each child is systematically approached, first with a clear vision of definite objectives that can actually be achieved, and second, through the use of simple, rapid, and reliable methods that can be widely applied. As far as scope and objectives are concerned we must recognize that there are some questions on this subject which are today beyond the power of answer; such questions must be set aside in favor of those that can be answered, and of the latter there are many which can prove to be illuminating and of practical worth.

A primary objective is to gather together the pertinent information which will enable us to assess the physical condition of a child. On this point nothing will count so much as an appraisal of his growth and development, for if this be satisfactory, his physical condition is obviously more favorable, whatever else may be wrong, than if growth and development have already been embarrassed. Even if susceptibility to disease were not increased, which it more than likely is, the child whose growth is good is clearly the better off. This must not be taken to imply that such a child is necessarily free from disease or from minor physical defects; indeed, he might have pneumonia, diabetes, a heart murmur or even real heart disease, a ragged tonsil, or some carious teeth. Under any of these circumstances one could only conclude that disease had not substantially affected his growth, *provided* that we had some method by which we could judge whether or not the child in question is up to par with respect to himself.

Thus, the chief clinical requirement of the problem is one of deciding whether a child, under the conditions of his life, is exercising and achieving his own native capacity for growth, and whether he is doing so on time. One may always choose to wonder whether that capacity might have been differently manifested in another home, another school, or state or climate, but practically speaking, speculation on the point is of little use as long as we must also admit that there are hundreds of adventures in daily life that might have turned out differently under other circumstances. Thus the question of whether a child (who has already done satisfactorily) could have done still better is far less consequential than the same question in the case of the child who has been demonstrably failing. Here at least we have the opportunity of undertaking a justifiable test of his capabilities by putting him into a more suitable environment, even one in which the chief change is psychologic rather than physical. As a last resort such a change could also be made for the child about whom we are in doubt, irrespective of whether his former record of growth and development happened to be good or bad. In either case, however, we shall not have a final or a complete answer, because we must again ask, what might have happened back home? Or at some other institution? Thus decisions on physical condition, or on growth and development, are to some extent indeterminate; the best that we can hope for is to decide whether growth and development and hence physical condition have or have not been satisfactory for a given child under a particular set of conditions. Even this problem requires systematic approach; it cannot be solved by simply making some measurements of the child and then comparing these with results on other children. Something much more fundamental to the child than his pounds or inches needs to be looked into and evaluated. Recourse to clinical ex-

perience will help to avoid the maze of entanglements that reside in even the simplest set of figures on heights and weights.

For the purpose of the present discussion, it is best to limit consideration to the events of growth and development that take place following infancy, or roughly from 2 to 20 years of age. This age period is of special importance today, partly because it has received comparatively scant attention from the pediatrician, certainly much less than it deserves, partly because the changes in preschool and school life are somewhat different from those in infancy, and partly also because knowledge of growth during infancy has already become an established and, on the whole, a fairly well-defined body of facts.

The singular uniformity and regularity of the growth process in infancy is matched only by that during intrauterine life; at least the magnitudes in either of these periods, being small, give the impression of greater regularity than one is wont to find on superficial examination of school children. If one is impressed with anything at all among the older group, it is the infinite variety and the correspondingly striking differences that may be found not only among children as a broad group, but even among those of the same age and in the same classroom. The tall, the short, the heavy, and the slender individuals are mixed in with those of more medium build; great differences are imposing among children in school, but similar differences are discovered among infants only after painstaking search. Certainly it is common experience that babies are much more nearly alike than older children; it is precisely the more numerous varieties of size and shape among older boys and girls that confuse the problem and seem to make it more complicated. Actually, however, the task of assessing growth and development throughout childhood can be greatly clarified in spite of the endless assortment of individual differences among this age group if a few guiding principles are systematically followed out. These have been embodied in what has been called the Grid technique, and, although full explanations of them cannot be given here, it is possible to illustrate and to summarize them briefly.

But in proceeding with this outline it must again be emphasized that the matter of growth and development is here approached and dealt with from the clinical and practical point of view. Some stress may very properly be laid on this point because we as pediatricians have not infrequently been accused of giving vague answers to parents, teachers, or others engaged with children, who sense that their questions, as to how a particular child is doing, penetrate down to the important issue of growth and its comparative satisfactoriness. On the other hand, how can we be helped by long tabulations of averages of selected groups of children, especially if the boy or girl before us did not belong to any of those original groups? It is discouraging, to say the least, to learn over and over again that there is 10, 15, or even 20 per cent variability among children in respect to various measurements that are traditionally made. Should there be any wonder that faith in measurements has fallen off to such an extent that they have even been discontinued in several places? The most carefully computed standard errors do not help us at all as long as these continue to be calculated by the highly objectionable though widely practiced technique of grouping children by age. No better way of introducing confusion into the picture of how growth and development operate could be devised. Yet, daily, we are confronted with the results of laborious efforts embodying the most meticulous work which prove to be of no avail in the practical applications of growth and development because age classification has totally obscured the really pertinent facts.

To get perspective as well as a more suitable working basis for the practical analysis and study of growth, we may consider an interesting paradox. It is supposed on general experience that the most descriptive feature about growth and development is *change*, especially change in body size as age advances. Accordingly,

it appears at first glance that, in attempting to study and to deal with growth on the clinical side, we must restrict ourselves to an examination of the *changes* which children display; for example, in their heights and weights. Emphasis on change in body measurements seems to come not only from the quite obvious fact that body size is altered by growth, but also because of the natural questions that are raised when a child fails to make his customary gains in height or weight. It is not normal that a child remain the same size from year to year, and if he does, complaints are soon brought forward.

Paradoxically, however, in attempting to judge the character of growth, we need to pay far less attention to the actual changes that accompany growth or that seem to define its external pattern than to certain still more fundamental items which in health remain quietly fixed throughout the long period of childhood development.

Now there are four attributes which characteristically remain fixed while Nature is acting to magnify a child's size during the ten or more years of school life: (1) physique or body build, (2) and (3) rate and schedule of development, and (4) the relation between basal metabolism and development. These four items may be called the "invariants of growth and development," and they form the framework for the scheme of analysis that is embodied in the Grid technique.

Let us test each of these items so as to gain further insight into their fundamental meaning and importance. Suppose that body build, instead of remaining constant, changes from year to year; what will be the result? Clearly, but one of two things can happen—either (a) the child becomes huskier and more robust than before, and, if this trend continues far enough, he will exceed the bounds of mere heft and turn out to be actually obese; or (b) he will shrink in bulk and assume the body characteristics associated with malnutrition. Suppose next that the child's rate of development is changed from the value of 1 level line per month that represents steady normal progress; again but one of two things can happen; namely, he must be speeding up or slowing down. Suppose again that he jumps from one schedule or timetable of development to another; the only result could be that he has either become more advanced or more retarded than before; and suppose finally that the relation between his metabolism and development is changed; in this case he must evidently have shifted his plane of heat production either to higher or lower levels than before.

Let us now apply these results to a simple example in order further to illustrate the significance which these four invariant attributes of growth and development possess. We may imagine before us a boy of 10 years of age, let us say, whose height and weight are so and so, whose hair is blond, and whose eyes are blue, who does not have dextrocardia or freckles but who did have measles at the age of 7. This fellow, we learn, dislikes cereals, and prefers two hours at football to one-half hour of music or Latin. A hundred other things might be said about him, many of which find their way into the medical record. But it is clear that we shall never be able to define him completely no matter how far we go in our description. From the practical standpoint of assessing his physical condition, we need to settle upon the *least* information which will suffice for our appraisal, and this incidentally is also a matter that is rarely given its proper phase of attention. Our procedure now consists of only two major parts:

I. *Appraisal of Growth and Development*
  1. *The Assessment of Physical Status*
    (a) Physique
    (b) Developmental level
    (c) Nutritional grade

2. *The Assessment of Physical Progress*
   (a) Channel course (shows change of physique, if any)
   (b) Age schedule (shows acceleration or deceleration of development, or neither)

II. *The Clinical Examination and Appraisal*
1. "Quick inspections" for minor defects in those who have passed I.
2. Intensive study—complete diagnostic investigations for those who have failed in I.

The only purpose of the Grid technique is thus to help carry through Part I—the appraisal of growth and development—and this is accomplished simply by reading a plot of heights and weights not in terms of inches or pounds but rather in terms of *physical status* and *physical progress*. Specifically, instead of asking how much a child weighs, how tall, or how old he is, we ask rather what has happened to his body build and is he developing on schedule. The answers to these questions give us an appraisal of growth, development, and nutrition, for it can be shown that under favorable conditions of health, growth and development take place (1) without alteration of physique, (2) at an average rate of 1 level of development per month, and (3) on a schedule specific for each child. In practice these conditions simply require that a child keep to his channel and to his own schedule of developmental advance. Failure to do so calls for more investigation by clinical means than is needed in the case of the child who passes the test of growth and development satisfactorily.

The application of these principles and results to large groups of children who cannot be given, and many of whom do not really need, complete physical examinations every year is evident. For if growth and development be appraised first and found to be satisfactory, it will only be necessary to search for comparatively minor physical defects. To this end, the benefits of the "quick inspection" may be utilized without the former risk of error, since the need for attempting to judge a child's "nutrition" has already been objectively taken care of through the ratings on physical status and progress. If, however, growth and development turn out in a given child, or in a group of children, to be unsatisfactory because physical status or progress, or both, are below par, we then know that the child must be referred for intensive study. The clinical examination may involve many laboratory tests, prolonged observation, repeated check-up on him and on his family, and thorough inquiry into the psychologic and social conditions of his life.

Moreover, if growth and development have failed, it is often possible to get an inkling as to the basic nature of trouble by differentiating clearly between the child whose physique is adequate but who is simply retarded in his development, a type which is often mistakenly regarded as being underweight and hence as undernourished. One will also be able to distinguish between the child whose growth failure through loss of physique and hence through consumption of body reserves has led him into simple malnutrition and the one whose unfavorable progress is due to more complex causes, for the response to change of environment in the former is invariably prompt and successful; in the latter, constitution, genetic background, and hence capacity to react may resist all remedial measures. In either case we shall have a uniform basis of comparison and in most instances a guide to further needs and study.

In this connection it is again well to emphasize that the present scheme for evaluating growth and development does not depend solely on structural elements, but that functional aspects in which the matter of growth is related to physiologic processes such as food requirements and basal heat production also play an important role. When a child has been found to be under par it is desirable that the method

which has pronounced him so should also provide a number of other means for investigating and testing his unfavorable condition. Besides, it is impossible on the clinical side to overlook the very immediate connections between food, metabolism, and growth. For these reasons comprehensive study has been devoted to this particular problem, the chief result of which shows that basal heat production depends solely on a child's developmental level, irrespective of his age or physique. This means that an obese boy in channel A_s+ at level 100 may be expected to have the same daily heat output as a slender lad at the same level in channel B_s or below, no matter whether they are of the same age or not. It means also, from another point of view, that when heights and weights are resolved into the two separate components of physique and developmental level (as they are when plotted on a Grid), metabolism can be accounted for entirely by that portion of height and weight which represents the child's development, and in addition, that the remaining portion representing physique has nothing at all to do with metabolism.

These results have been recently reviewed with the aid of newer data, especially from Johnston's series on obese girls and Webster's on normal children. Somewhat over 1,000 observations on girls alone now turn out to have mean values which cannot be statistically distinguished from the Grid standards originally published. The coefficients of variation run from 4 to 11 per cent, and the trend line over the entire range from 2 to 20 years is precisely the same as before. These results are now being prepared for early publication. They may be mentioned, however, owing to certain misunderstandings which have arisen in connection with the important relations between growth and metabolism.

To summarize it may thus be said that the clinical problem of growth and development involves much more than the purely structural features connected with body size and shape, or even with the cold data on height and weight. It ramifies, in fact, into every phase of child life; and for the pediatrician who is called upon to deal with children directly, the evaluation of growth and development constitutes a large and, in many respects, even the dominant part in his appraisal of their physical condition.

QUESTION.—Will Dr. Wetzel tell us, as the number of calories are the same for different channels right across, whether this is really reliable?

QUESTION.—How do you determine into which channel the child goes, whether he is fat or skinny? It would be rather hard to determine where that child should go.

DR. WETZEL.—The best and safest way to decide whether a child is in his proper channel is to see, from serial observations, whether he has continued or is continuing to follow that same channel at such a rate that he progresses one level per month. One thus has, in reality, a double check on the child, for satisfactory development can be achieved only when (1) a child keeps to his channel (which means that he is neither gaining nor losing physique) and also (2) when he keeps to his schedule of development by paralleling one of the neighboring auxodromes. The latter fact guarantees that he is "progressing on time" and, therefore, that he is neither speeding up nor slowing down. There are but few exceptions to this very general rule, and they can be identified only by deliberately changing the circumstances of a child's life and by then observing whether the child reacts with a definite shift of channel or auxodrome because children who are doing satisfactorily cannot easily, if at all, be budged from their natural channel and schedule, whereas the child under par will respond to favorable changes in his environment by definite and sometimes by even enormous shifts in channel and auxodrome as he is being returned and restored to par.

While awaiting further information from subsequent follow-up, one may get a partial answer by remembering that from 60 to 70 per cent of children fall

within the three center channels. I, myself, am most concerned about the B_2 group, not only because these youngsters are actually closer than the center group to the verge of becoming under par, but rather more because they represent the type of child upon whom a dozen examiners will disagree most often, half of them assessing the child as satisfactory, whereas the other half will evaluate the same child as being unsatisfactory. The children in the B_2 group, in other words, represent the greatest puzzles because they are neither definitely good nor definitely bad; they need, consequently, to be kept under frequent surveillance. Thus if a child falls into the center channels he is certainly near average and presumptively in good shape, although he might, nevertheless, be subject to a disease that has, however, not yet produced any serious effect upon his growth and development. If a child falls into the B_2 group we ought to look at him much more closely than if he is in M, A_2, A_1, or even B_1. We must concentrate on the children in B_2 and below and if we find within a year or so that they continue in this channel at the rate of one level line a month, we may conclude that they probably have as much right to that channel as the youngsters in any other channel have in theirs.

(*Demonstration on blackboard.*)

Now as to the reliability about the metabolism values—the way we estimate and, in reality, predict a youngster's basal metabolism from the Grid is to read the daily caloric heat output that corresponds to his level. A boy's caloric output is always a little higher for the same level than that for the girls. The reason one gets more reliable estimates from the Grid standards is because this method makes proper allowance for height and weight by resolving a certain fraction of both height and weight into the body build component; that is, into physique which is, so to speak, nonmetabolic and into another component, developmental level, which accounts entirely for heat output. This explains the great difference in metabolism which one finds among children of different levels even though they have the same height or again the comparative equality in heat output among children of widely different physiques whose height also varies greatly. We get the least variances and, therefore, the greatest reliability in prediction when we allow, as the Grid does, for the fundamentally different effects of physique and level on metabolism.

CHAIRMAN JOHNSTON.—To me, Dr. Wetzel's Grid offers a simple method of recording graphically the nutritional progress of a child. The exceptions which I noted in the introduction to the parallelism between weight and the retention of basic substrate were relatively short-time observations in terms of the total growth span, though some of them cover approximately a year, and I doubt that a loss of nitrogen and calcium over any longer period would fail to be reflected in the Grid rating. The practical application of his grid was interestingly made in the study of a large group of children with first infection tuberculosis. We have previously shown that a certain number of these can be expected to develop endogenous reinfection, and that in many instances the precipitating factor is malnutrition. In a group of approximately 1,000 of these children, we have observed about thirty-seven reinfection lesions. When the exciting incident is malnutrition, the Grid gives a helpful warning by recording a departure downward from the child's usual channel.

It is perhaps premature to comment on his calculations of the expected basal calories, but in our experience these fit acceptably with clinical findings and particularly in the case of obesity. The false low rate resulting from the use of a surface area standard for this group of children is now widely recognized, as is the irrationality of the use of thyroid to effect reduction; calculated against this standard, the rates are for the most part normal or elevated. These data are to be published separately.

We are not yet in a position to draw any valid conclusions from parallel studies of physical and mental growth. It is one of the many things that we hope will be possible from the longitudinal studies now in progress throughout this country. There is a suggestion from Weech and Campbell that growth and development may actually bear a reciprocal relationship at least in so far as motor behavior goes. Dr. Anderson will give us some of the results of the studies at the University of Minnesota on mental growth which have a special value because of the span they cover.

DR. ANDERSON.—In the use of mental tests for practical purposes, concern is not so much with present status as with the prediction of later status and especially of status after development is complete. This is true with problems of adoption, the assignment of children to special classes, the selection of children for permanent institutional care, and many other problems of diagnosis and prognosis.

Recently I correlated the results of tests given periodically in longitudinal studies with the final measures reported and also back with the first measures of status. This problem can only be attacked when substantial series of tests on the same children over a long period of time are available. It is characteristic of mental growth that the individual does not lose what he has already gained, but moves on from that point to add to what he has. While there is the possibility of loss in some functions, data in general indicate that the gains during the developmental period far exceed the losses. The size of the increment for any period of time decreases as maturity is approached. Note that we are not concerned with the use of mental tests to indicate changes in mental growth paralleling changes in physical growth but are concerned only with the predictive value from any measurement to future status.

The results clearly indicate that the earlier in the developmental period the child's capacity is tested, the less accurate is the prediction of his final status. The later in the period of growth his test is given, the better is the prediction of final status. Undoubtedly this principle also holds with respect to physical growth. The underlying mathematical principle is based upon the principle that as the size of the part which goes to make up the final whole increases, the greater is the correlation between it and the whole. Thus, a prediction at the age of 2 years in which 30 per cent of total mental growth is completed is much less accurate than a prediction at the age of 12 years, when 80 per cent of growth has been obtained. The formula which governs this relationship is the formula that r square equals the per cent of overlap between the part and the whole.

The conclusions reached indicate that intelligence tests measure a pattern of functions which change with age. Correlations with initial status steadily decrease, while correlations with terminal status steadily increase. A significant change in relationship occurs at about the age of 18 months, when the symbolic functions represented in the use of language appear. Both because of this and because of the relations already described, tests made in early infancy are of relatively little value in predicting final status. Tests made after the age of 18 months and up to the age of 3 years are of some value; tests made between the ages of 3 and 7 years are of substantial value, and after the age of 7 years very good predictions can be made of terminal status. Moreover, from experience with mental tests given to young children, it is known that various conditions, such as motivation, negativistic responses, and the difficulty of obtaining rapport tend to pull down individual children's performance in such a way that the actual test results may be only a poor approximation of what the child can do under the best possible conditions of motivation and interest. The younger the child, the greater the skill is necessary for making a good examination and the more alert the examiner must be to the problems of rapport and motivation.

Because of the limitations of single tests on young children and because of the value of securing observations over a period of time in order to determine the direc-

tion of the growth process, it is recommended, where definite practical action has to be taken with young children, that two tests separated by an appreciable amount of time (three months is desirable) be given and the conclusion with regard to the child be based upon the results of both. Our results indicate that despite the value of tests in indicating present status and future potentiality, substantial care and caution must be exercised in the interpretation of the results in the individual case, and especially so with very young children.

DR. H. CHANDLER CLARK, NEW ROCHELLE, N. Y.—With reference to the relation of mental age to adoption, at what age should the mental growth rate be determined? I understand it should be at least 2½ years.

DR. ANDERSON.—At the present time I would say at least 2 years of age. In the future it may be possible for us to make such prediction earlier by more careful selection of the tests in accordance with the principles developed in my paper. For children under 2 years, we have some evidence that shows that knowledge of the characteristics of the true mother and true father make a better prediction than existing tests. Especially is the rate at which the true mother went through school, i.e., her age at time of completing, say, the eighth grade, of value. Infant tests, however, will screen out extreme retardation but are not so good for indicating acceleration. The later the test is given, the better the prediction.

QUESTION.—What should be the minimum age if you do not know the parents?

DR. ANDERSON.—If you want my opinion, I would set no minimum age. The ideal procedure would be that of placing the child on trial in the foster home for six months or a year. You would then be in a position to observe that child in the home and obtain successive determinations of his status. Many of us are familiar with the tragedies which occur at 10, 12, or 14 years, where there has been poor placement. The whole program of prediction is one of great difficulty. If we had good measures for the very early ages, say below 12 months, the procedure would be relatively simple. Unfortunately, we lack such precise measures.

QUESTION.—Is there a correlation between head size in early infancy and subsequent growth? One might predict retardation in the child who is slow in achieving head growth. I have seen unfortunate adoptions in which the child's retardation could have been predicted from the size of the head.

DR. ANDERSON.—Personally, I am not aware of any scientific literature on that problem. It might be well worth some study, but judging from the literature on the relation between head size and intelligence in older persons, I am a bit skeptical as to a relation.

QUESTION.—You said that intelligence and verbal fluency were not the same. What criteria can you use to separate the two?

DR. ANDERSON.—I probably was a bit too brief in my exposition. What I meant to point out was that intelligence is not the same as verbal fluency but rather is related to the capacity to use symbols effectively. In developing a test, we try to use items that measure more than one factor. Some people who are not verbally fluent are very intelligent, even though language facility and intelligence are connected. I did not want you to interpret intelligence as synonymous with language ability but as related to it. What is important is the ability to deal with the external world and experience through symbols, i.e., the ability to represent and manipulate experience.

CHAIRMAN JOHNSTON.—From a fifteen-year experience with a very large group of foster home child candidates for adoption, I feel very strongly the importance of the point which Dr. Anderson makes. I have been particularly impressed with the importance of repeating a number of times a child's mental measurements after he has been placed in a sympathetic environment and have seen the marked improvement which frequently follows the change from the usual hectic home which occasioned his need for care by a foster home agency.

Some of the Controllable Items Affecting Growth

Julian D. Boyd, Iowa City

In any large group of children, one can find various patterns as to physique, size, and rate of growth. To what extent do these deviations represent the expression of inborn tendencies and to what extent do they reflect the effect of past or present environmental factors? The answer to the question will determine whether the physician need have concern in relation to growth during childhood. If growth depends solely on the unfolding of one's hereditary pattern, growth and physique compose problems of genetics alone. If instead, growth is determined significantly through environmental factors, then the rate, quantity, and quality of growth may be used by the physician as gauges of the quality of the child's conditions of life. Few will question that both heredity and environment contribute significantly to the nature of the growth process.

One may define growth-controlling agencies in terms of their time of effect. The ultimate capacity for growth will be determined and will be limited by hereditary factors. These factors relate, however, to the qualities of the germ plasm rather than to the stature of the parents: Often we see children whose rate and quality of growth exceeds that of either parent. We may assume properly that the individual never will exceed the limits of growth predetermined by his germ plasm. Nevertheless, whether he achieves fully his inborn pattern for growth will be determined by postconceptional conditions: by the favorable or unfavorable factors in his environment throughout his period of development. Few of us ever attain or maintain the ideal of physiologic environment; even in the absence of outspoken deprivation or of disease, most persons have sufficient "misadventures with health" to affect themselves adversely. Therefore it is a reasonable premise that few of us ever achieve our innate capacity for growth and development. According to this view, observed levels of growth reflect the balance between innate propensities for growth and the limiting effects of adversity. If such assumption is justified, then we should not accept observed levels of growth in individual children as satisfactory or desirable until we have ruled out the existence of unfavorable environmental factors. With the child whose growth pattern equals or exceeds that observable in favored children, one need have no immediate concern as to growth. On the other hand, the child who falls significantly below the average child should not be dismissed lightly on the basis of genetic factors until his manner of living and his level of health have been examined critically. Desirable patterns of growth, similarly, cannot be defined on the basis of average levels of attainment; they should be measured on the basis of attainment levels among those whose manner of living is as free from recognizable handicaps as can be assured. The pattern of growth for child populations of similar genetic stock can vary significantly when different levels of environment control prevail.

To illustrate variations in pattern of growth between different groups of children, one is justified in expressing growth attainment in terms of height for age. Body length cannot serve acceptably as an index of the totality of growth; it certainly is acceptable as a measure of linear growth of the body skeleton, however, and thus serves as a coefficient of total growth. Using height in this manner, let

us compare the attained stature in terms of age for several groups of children, as illustrated in Fig. 1.

The basic curve relates height and age for 1,243 boys living in Iowa City (1920-1934). In the words of the observer, from whose publication the data were borrowed,[1] the group "may be characterized as homogeneous with reference to geographic location and sex, not significantly diverse racially, and somewhat favored economically and culturally." The midline, *M*, represents the mean value for height for the corresponding age; the two outer lines, *+1* and *-1*, embrace two standard deviations, or more than 68 per cent of all children examined for any given age level. In other words, less than 16 per cent of the total group fell below the lowermost, *-1*, level. One may infer that those whose values fell in that lower zone were

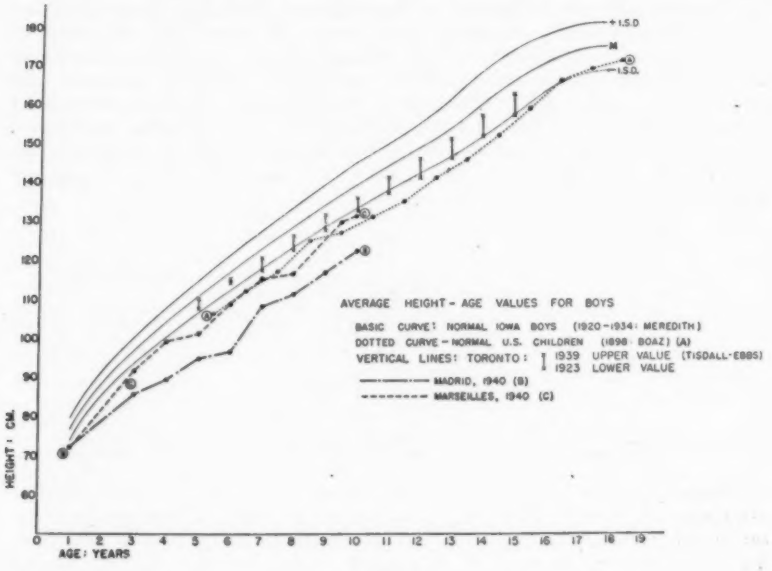


Fig. 1.

less favored than other members of the corresponding age group. These curves for Iowa City boys will be used as representative of what may be expected in a group of children living under similar conditions of life and will be used as a basis for comparison for the children whose growth is illustrated by the other curves on the diagram.

Curve *A* offers the average values reported by Boaz[2] in 1898 for boys from various parts of the United States and Canada. Racially these boys probably did not differ significantly from the Iowa City boys: they do represent inconstancy of geographic locality, socio-economic level, and era. Note that almost throughout, the average values for Boaz's subjects fell into the lowermost 16 per cent of the Iowa City values.

The vertical lines relate to two sets of measurements of school boys from Toronto, Canada[3]: the lower limit of each line represents average height for age observed in 1923; the upper limit represents corresponding values for school boys of the same age in 1939. Genetically and geographically the two groups do not differ, yet the average values for height are significantly different. Note further that the

1923 values are somewhat in advance of those reported by Boaz (curve *A*), and that the 1939 values approach the mean values for the Iowa City boys (curve *M*).

Curves *B* and *C* represent the average values observed in two groups of boys living under conditions of marked and recognized adversity: children from Marseilles and from Madrid, respectively.[4, 5]

The foregoing comparisons are presented as evidence that environmental factors can alter certain growth patterns significantly in groups of similar genetic shock. This fact has practical importance in the physical appraisal of every child. The examiner should correlate the child's growth status with standard tables to determine his rank. The examiner should not accept substandard growth as normal for the individual or as desirable, until he has ruled out the existence of unfavorable states in the child's health or manner of living. It is desirable to compare the child's status with values observed in favored groups rather than to use those that relate to general child populations. Most of the published tables are based on measurements of large child populations, including a high proportion of those living under conditions unfavorable for their best growth. When the physician uses such tables as guides in his appraisal, he is handicapped in two ways: (1) by the use of inferior standards and (2) by his tendency to rationalize his observed measurements as normal rather than to question whether they are up to the desirable level for the individual child. Such a policy of laissez faire is not in harmony with modern concepts of preventive pediatrics.

TABLE I

PREVALENT LEVELS OF LINEAR GROWTH IN TERMS OF AGE FOR CHILDREN LIVING UNDER CONDITIONS OF COMPETENCY

36 in.	(3 ft.)	by	2½	yr.
42 in.	(3½ ft.)	by	5	yr.
48 in.	(4 ft.)	by	7½	yr.
54 in.	(4½ ft.)	by	10	yr.
60 in.	(5 ft.)	by	13	yr.

There should be an average gain of 2½ inches yearly between the ages of 2 and 12 years; gain of less than 2 inches during any year should be viewed with concern.

Certain landmarks relating to growth in height should be fixed in the mind of every examiner of children, so that he can sense the degree of conformance of observed measurements with that to be expected under reasonably favorable conditions. Table I has been prepared to meet such a need. It applies both to boys and to girls between the ages of 2 and 13 years. Most children who have lived under favorable conditions will meet or will surpass the stated values. Note the regularity of increment of age and of height.

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QUESTION.—Can you take a little fellow and stimulate his growth or check the growth of a taller one?

CHAIRMAN JOHNSTON.—This brings up the question of hormones which cannot be discussed at length in the limited time available. We should not think

of any one of the hormones as specifically controlling growth. Prior to 1922 diabetics never matured physically; they did not live beyond puberty. You cannot isolate a single hormone and say it controls growth. It is possible to have a defect in none of the hormones without there occurring at the same time a change in the entire endocrine system, and it subsequently becomes impossible to state the primary lesion.

The existence of a separate hormone controlling growth is questioned, though Kamm has isolated a principle, probably not pure, capable of stimulating the growth process. In our hands this has not had clinical usefulness; the anabolic effect on nitrogen reported by Gaebler could be duplicated, but presumably the development of antihormone was prompt and rendered futile a repetition of the injections. Others, however, have reported a stimulation of growth by its use. Gigantism and acromegaly are both established as associated with overactivity of the anterior lobe. The clinical problem posed by a generalized retardation of growth must include a consideration of lesions of the anterior lobe, and there is the case of a child, on whom a record of heights and weights was kept, who at autopsy showed a tumor of this region and whose parents' concern over a number of years was a retardation in the rate of her growth. Mentally the child was advanced. Headache was a terminal symptom.

(*Slide.*)

The role of the thyroid gland in affecting growth and development is on firmer ground, though the fact that it influences all oxidative processes makes it more likely that its growth-promoting effects are nonspecific. The retardation of growth accompanying the hypothyroid state is characterized by an inability to retain both nitrogen and calcium, but negative balances for both of these items are seen in the hyperthyroidism also. Mild degrees of the latter state show accelerated growth, the result of an increased anabolism generally. The pertinent point is made that optimal retention and therefore growth occur at a normal metabolic level and that departures from this level in the direction of either the hypo or the hyper state are inimical to normal growth. Probably all other glandular processes depend also on this normalcy, and it is notable that the approach to a correction of a presumed defect in those hormones concerned with sexual development involves first an evaluation of thyroid status. When the problem of retarded growth or development presents itself in the younger age groups in whom metabolism determinations are not feasible, we have found greatest usefulness in the assessment of skeletal age from the roentgenogram of the wrist, though others have stressed the usefulness of measuring phosphatase and cholesterol.

From a practical clinical standpoint, probably the factor of greatest importance in influencing growth and development in the middle economic strata of our population within the limits that growth can be influenced by heredity is the occurrence of a disease process influencing unfavorably the utilization of the diet. The effect of focal infection on the utilization of nitrogen we have demonstrated repeatedly, and the problem exposed by a failure of normal growth by a child who is refusing an adequate intake of food is more likely to involve the detection of factors such as chronically infected tonsils, teeth, or sinuses or the discovery of unsuspected tuberculosis or rheumatic fever than it is the supplying of missing items in a defective diet. Our nutritional surveys would be worth much more if this factor were taken into account. In daily clinic practice the presence of some disease process accounting for growth retardation is, in my experience, ten times as frequent as an inadequate diet.

DR. W. W. GREULICH.—I want to preface what I have to say about Dr. Wetzel's Grid with a well-deserved tribute to his work. Dr. Wetzel, in my opinion, deserves a great deal of credit for calling to the attention of the medical profession the necessity of following the growth of individual children over a period of time.

All students of human growth and development are aware that single determinations of height and weight in children have a very limited value. If one wishes to know how an individual child's growth and development are progressing, one must make repeated measurements of that child over a period of time in order to find out. Dr. Wetzel's Grid represents a very laudable attempt to make height-weight-age data more meaningful than they have been in the past. His formulation represents a tremendous amount of thought and labor, and it puts all who are interested in human growth and development in his debt.

Height-weight-age data, however, have certain inherent limitations which neither Wetzel's Grid nor any other scheme which has thus far been suggested can remove. In a population as heterogeneous in national antecedents as that of most parts of this country, those limitations are especially marked and important. Given two boys of the same age, weight, and height, one might conceivably be an individual who, because of something approaching optimal environmental conditions, is realizing the full developmental potentialities of his genetic constitution, while the other may belong to a larger statured strain but whose growth and development have been, at least temporarily, retarded, because of some serious illness or other environmental misadventure.

Wetzel's Grid, in a somewhat clearer fashion than ordinary curves of height and weight, shows that some children grow rapidly while others grow at a distinctly slower rate. Wetzel's channels indicate the velocity of growth in individual children. But it is not enough to know what path a child is following toward maturity; what is significant is to know, at any given point in time, how far the child has traveled toward maturity and how the amount of progress which he has made during his lifetime compares with that made by other children of the same age and sex.

Height and weight alone or together are, in last analysis, significant not in themselves but principally because they provide some index of progress toward maturity. At least they enable us to compare a given child with others of the same sex and age. As mentioned previously, such comparisons can easily be misleading, especially in a population like ours. One difficulty in using height and weight as an index of progress toward maturity is that we do not know what the ultimate height of an individual is going to be and hence we cannot compute at any given time how much progress he has made toward that goal.

The x-ray study of the skeleton does provide a means of determining the developmental status of a child at any single point of time. The sequence of osseous development, especially in the hand and wrist, is now well known, and a single film of a child enables the pediatrician to determine very objectively how far skeletal development has progressed. During recent years a large body of data on the skeletal development of apparently normal children has been collected, notably in the Brush Foundation Study begun by the late Dr. T. Wingate Todd. Todd's standards of skeletal development represent a pioneer attempt in this field, and the revision of those standards, which is now in progress, will provide an Atlas of even greater utility.

In studying the growth and development of children, we are in much the same position as the three blind men who encountered the elephant. There is constant danger of each of us attributing more importance to information elicited by the techniques with which he is familiar than is justly deserved. In my opinion, no single technique, be it Wetzel's Grid or skeletal assessment, is of itself entirely adequate for the purpose. It is only by pooling our resources, by employing various techniques—always with due allowance for their limitations—that we can hope to advance significantly our knowledge of this interesting and important field.

News and Notes

Written examinations for candidates appearing before the American Board of Pediatrics will be held on Oct. 8, 1943. Instructions to candidates for the examination will be issued from the office of the secretary in due time.

Oral examinations will be conducted by the Board in New York City on Nov. 20-21, 1943, and in Cincinnati, Ohio, on Dec. 11, 1943.

Final notice is hereby given by the American Board of Pediatrics that on, and after, July 1, 1943, candidates who have heretofore been classified in Group I will no longer be accepted. On that date all candidates will be on the same basis, and no special consideration will be available to candidates who have been in practice ten or more years. All such individuals who are contemplating filing application before the Board must do so before July 1.

The following applicants were certified by the American Board of Pediatrics at the Examinations in St. Louis, March 27 and 28, 1943:

Dr. Egbert Vernon Anderson, 25 W. Chase St., Pensacola, Fla.
Dr. Henry L. Barnett, 500 S. Kingshighway, St. Louis, Mo.
Dr. Lester Edward Bower, 4603 N. Western Ave., Chicago, Ill.
Dr. Joseph Alfred Carbone, 504 Broadway, Gary, Ind.
Dr. Harry H. Clemens, 725 4th St., Marysville, Calif.
Dr. John Henry Doval, 500 S. Kingshighway, St. Louis, Mo.
Dr. C. Hall Farmer, 553 Walnut St., Macon, Ga.
Dr. Anita Edith Faverman, 760 Market St., San Francisco, Calif.
Dr. Alexander N. Freed, 10465 Carnegie Ave., Cleveland, Ohio.
Dr. Morton J. Freedman, Peoria, Ill.
Dr. Lawrence Eddy Goldman, Lister Building, St. Louis, Mo.
Dr. Charles F. Good, 10515 Carnegie Ave., Cleveland, Ohio.
Dr. Salmon Reclus Halpern, Dallas, Texas.
Dr. Martin J. Harris, 321 W. Broadway, Louisville, Ky.
Dr. Alex Klinkowstein, Children's Hospital, Detroit, Mich.
Dr. W. Wayne Lockwood, 602 W. University, Urbana, Ill.
Dr. Harold D. Lynch, 216 S. E. Riverside Dr., Evansville, Ind.
Dr. Ruben Meyer, 10 Peterboro St., Detroit, Mich.
Dr. William G. Motel, 5304 S. University Ave., Chicago, Illinois.
Dr. Charles Eugene Muhleman, LaPorte, Indiana.
Dr. Wesley Stephan Nock, 1800 Wilson Ave., Chicago, Ill.
Dr. L. Paul Rasmussen, 516 Boston Bldg., Salt Lake City, Utah.
Dr. Edith C. Robinson, 5065 Waterman Ave., St. Louis, Mo.
Dr. Margaret Mary Scannell, P. O. Box 310, Indianola, Miss.
Dr. Lloyd M. Simonson, 1001 N. 8th St., Sheboygan, Wis.
Dr. Eugene A. Stack, 5955 W. North Ave., Chicago, Ill.
Dr. George Ewing Stafford, Salina, Kan.
Dr. C. S. E. Touzel, 1324, Summit St., Fort Worth, Texas.
Dr. Robert A. Trombley, Albuquerque, N. M.

Dr. Ly Werner, 314 First National Bldg., Albuquerque, N. M.
Dr. Thelma Marie Wygant, 651 Fisher Building, Detroit, Mich.
Dr. Melvin Francis Yeip, 10824 St. Clair Ave., Cleveland, Ohio.

The following applicants were certified by the American Board of Pediatrics at the Examinations in New York City, April 23 and 24, 1943:

Dr. Hattie E. Alexander, 3975 Broadway, New York, N. Y.
Dr. George King Anderson, 2101 Constitution Ave., Washington, D. C.
Dr. Katherine Bain, Children's Bureau, U. S. Department of Labor, Washington, D. C.
Dr. Edward E. Brown, 42-02 Layton St., Elmhurst, N. Y.
Dr. Eliza Hunton Caldwell, 346 Corlies Ave., Pelham, N. Y.
Dr. Hugh A. Carithers, Jr., Jacksonville, Fla.
Dr. Merl John Carson, State Board of Health, Raleigh, N. C.
Dr. J. Frederick Close, 66 Milbank Ave., Greenwich, Conn.
Dr. Samuel Dillon, 119-02 Rockaway Beach Blvd., Rockaway Park, N. Y.
Dr. Frank A. Disney, 420 Arnett Blvd., Rochester, N. Y.
Dr. Raymond George Filsinger, 267 Linwood Ave., Buffalo, N. Y.
Dr. Nathan Michael Greenstein, 1488 Metropolitan Ave., New York, N. Y.
Dr. Alexander D. Gross, 9034 214th St., Queens Village, N. Y.
Dr. Edward Adams Hardy, 346 Corlies Ave., Pelham, N. Y.
Dr. Frederic Sargent Huntington, Middlesex and Hollow Ree Rds., Darien, Conn.
Dr. Roswell Dorr Johnson, 70 Howe St., New Haven, Conn.
Dr. Nathan Robert Kahn, 255 Eastern Parkway, Brooklyn, N. Y.
Dr. Arthur A. Kaplan, 270 Genesee St., Utica, N. Y.
Dr. Ruskin King, 201 E. Hall St. (after May 16, 1943, 10 W. Taylor St.), Savannah, Ga.
Dr. William Howell Kiser, Jr., 33 Ponce de Leon Ave., N.W., Atlanta, Ga.
Dr. Isidore Leber, 43 Lefferts Ave., Brooklyn, N. Y.
Dr. Ethel Margaret MacLean, High Street, Farmington, Conn.
Dr. Israel J. May, 73 McKibben St., Brooklyn, N. Y.
Dr. Emerson K. McVey, 42 E. 112th St., Chicago, Ill.
Dr. David Merksamer, 105 Lincoln Rd., Brooklyn, N. Y.
Dr. Edward S. O'Keefe, 31 Broad St., Lynn, Mass.
Dr. George Edward Oosterhous, 113 N. Carroll St., Madison, Wis.
Dr. Irving B. Richter, 3403 W. Lawrence Ave., Chicago, Ill.
Dr. Meinhard Robinow, University of Georgia School of Medicine, Augusta, Ga.
Dr. Frederick Peckham Rogers, 785 Farmington Ave., West Hartford, Conn.
Dr. Lewis J. Schloss, 50 East 78th St., New York, N. Y.
Dr. Jacob J. Schneider, 1511 Union St., Brooklyn, N. Y.
Dr. Annie V. Scott, 7 West Gramercy Park, New York, N. Y.
Dr. Benjamin Stein, 1835 Eye St., N. W., Washington, D. C.
Dr. Daniel Michael Tolmach, New York State Reconstruction Home, West Haverstraw, N. Y.
Dr. Ethel H. Trygstad, Carlton Ave., Central Islip, N. Y.
Dr. Edward V. Turner, 15 N. 5th St., Wilmington, N. C.

Dr. Elizabeth Ufford, 34 Ivy Way, Port Washington, N. Y.
Dr. Rudolph E. Vandeveer, 414 N. Washington St., Rome, N. Y.
Dr. Martha Cook Wager, 111 East 71st St., New York, N. Y.
Dr. Frank Strattan White, Teaneck, N. J.
Dr. Gladys Claire Winter, 805 Red Rd., Teaneck, N. J.

On April 20 and 21, in connection with the meeting of the Missouri State Medical Society, a pediatric conference was conducted by the Division of Child Hygiene of the State Board of Health and the Missouri members of the American Academy of Pediatrics.

In the day-and-one-half conference the following topics were discussed:

"Child Behavior," Dr. Paul E. Kubitschek.
"Home Examination of a Well Child," Dr. Park J. White.
"Early Clinical Signs of Dietary Deficiencies," Dr. Alexis F. Hartmann.
"Formulas for Well Babies," Dr. Jerome Diamond.
"Recommended Procedures for Active Immunization," Dr. Chester J. Antos.
"Sulfonamides in Children's Diseases," Dr. Henry L. Barnett.

The conference was attended by a number of general practitioners, chiefly from the rural parts of the state.

Book Review

Nasal Sinuses: An Anatomic and Clinical Consideration. O. E. Van Alyea, M.D., Baltimore, 1942, The Williams and Wilkins Co., 262 pages. Price, $6.50.

This work is largely the result of the author's anatomic studies and clinical observations during the past several years. The book will be a welcome addition to the literature on nasal sinuses and should prove interesting and useful to pediatricians.

One of the most striking features of the book is the illustrations. They are all original and include both colored and half-tone illustrations, diagrams, and line drawings. The reproductions of roentgenograms are unusually clear and helpful. There are many photographs, both plain and colored, colored microphotographs and also many of gross specimens from the author's anatomic studies. These are unusually clear and will add greatly to the value of the book. The material discussed is divided into chapters on general histopathology, acute nasal infection, and individual chapters on each sinus. The sinuses are discussed especially from the standpoint of their origin and development and the author's own anatomic studies. This discussion is the essence of the author's personal contribution to the subject. Also, in the chapters on individual sinuses there are discussed both diseases and their treatment, especially surgical correction. There are also short chapters on sinus disease in children, allergy, and surgical and nonsurgical treatment. The known surgical treatment discussed includes intranasal medication, physical therapy, the use of foreign protein, and a rather sketchy presentation of the use of the sulfonamide drugs.

Much of the material includes quotations from the literature and in certain areas amounts to a brief critical review of the subject.

Wherever the author presents his own work the text takes on a refreshing and instructive atmosphere. It is suggested that he should have included a discussion of the ear in children, since, at least from one standpoint, this organ may be considered a part of the sinus system of the head.

The book is in good form, has an ample bibliography, and will prove invaluable as a reference work to current ideas on this subject.

McCULLOCH.

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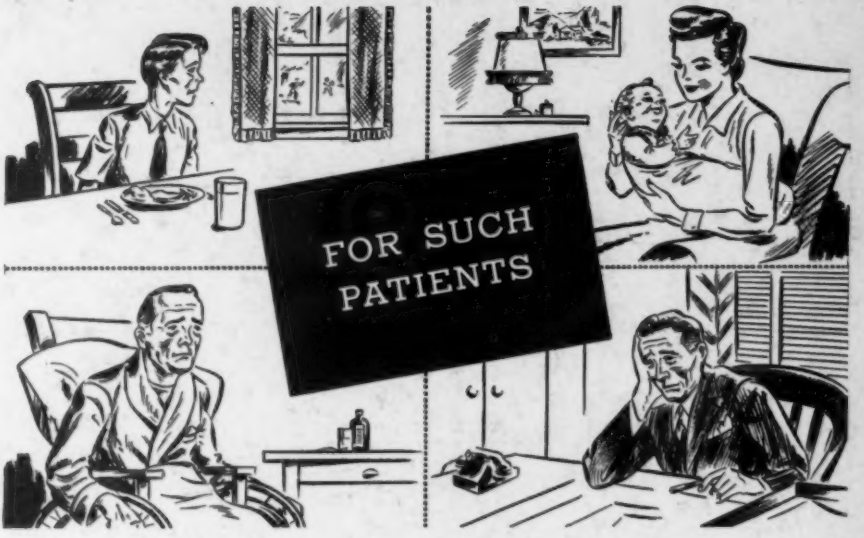

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